INFANTILE SPASMS

Diagnosis, Management and Prognosis

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Preface

This monograph provides a comprehensive and critical review of current knowledge regarding infantile spasms (West syndrome). While the devastating manifestations of this epileptic disorder of infancy and early childhood have stimulated a wealth of clinical research over the past 30 years, the etiology remains unknown, the pathophysiology is poorly understood, and the optimal course of treatment is controversial. The primary goal of this book is to carefully assess all aspects of the disorder, and to provide the reader with a concise guide to the most effective and efficient means for establishing the diagnosis, formulating an appropriate treatment plan, and assessing the outlook for long-term outcome. We believe that pediatric neurologists, general pediatricians and clinical neurophysiologists, will find the book particularly useful as a readily accessible source of authoritative information on all aspects of this syndrome. Other clinicians that provide specialized care for children with this disorder will find specific information regarding associated manifestations and side effects of therapy. A secondary, but equally important, goal of this monograph is to provide a compact and structured knowledge-base which can be used to facilitate the development of future research protocols designed to uncover the basic mechanisms underlying this disorder and lead to more effective treatment modalities.

Our interest in infantile spasms began more than 25 years ago. Since then, we, and our colleagues at Baylor College of Medicine, have conducted a series of clinical investigations directed toward improved diagnostic methods, better understanding of the pathophysiology underlying this disorder, and the establishment of more efficacious therapeutic regimens. While the information we have learned clearly has played a major role in the organization and structure of this monograph, our intent here is to provide the reader with a balanced and comprehensive assessment of each topic considered. Consequently, we have attempted to present the results of all research studies in a neutral and unbiased form that allows the reader the opportunity first to formulate an opinion based solely upon the facts. In the case of clearly conflicting or confusing research results, and other controversial issues, we then provide the reader with a tentative guide or resolution based upon our own perspective.

In the initial chapters of this monograph (Introduction and History) we characterize the syndrome, provide an overview of the manifestations, and briefly summarize the history of the disorder up to 1960. (An extensive and more

detailed review of the early literature was published in 1976 by J. R. Lacy and J. K. Penry, and their monograph remains a valuable resource.) In subsequent chapters we explore in detail the more recent research findings and clinical reports concerning infantile spasms. The epidemiology of this disorder is reviewed to provide estimates of the incidence, relationship of onset to age, and familial characteristics. The clinical manifestations of the disorder are discussed extensively, including modes of presentation, spasm frequency, and patient classification. Electroencephalography (EEG) plays a major role in both the diagnosis of this disorder and in assessing the response to therapy. Consequently, the proper use of EEG is emphasized and detailed, and the variations of both the ictal and interictal patterns are presented. The role of other diagnostic techniques such as CT, MRI, and PET in the evaluation of patients with this disorder is evaluated, and their value in assessing prognosis is considered. We review in some detail the differential diagnosis of infantile spasms, and also discuss a number of related syndromes. Seizures of other types may co-exist with infantile spasms, or can appear later after spasms have ceased. This topic is reviewed both with respect to the potential problems it creates for correct diagnosis, and in terms of the significance for better understanding the underlying pathology. While the etiology (or etiologies) of West syndrome are still not known, a number of predisposing factors have been identified. This subject is considered in depth, and a variety of potential etiological mechanisms are explored. Similarly, the pathophysiology of this disorder is still unknown, although many potential mechanisms have been proposed including brainstem dysfunction, focal or diffuse cortical abnormality, abnormalities of brain maturation, metabolic dysfunction and immunological defects. The various possibilities that have been proposed are compared, and areas in which additional specific studies are needed are identified. Perhaps no other aspect of this disorder has created as much controversy as that of therapy. Although a great many studies have been published over the past 50 years, there is still no widely accepted standard of care. We review the currently prevailing opinions concerning treatment, including hormonal therapy (ACTH and corticosteroids), anticonvulsants, pyridoxine, immunoglobulins, thyroid releasing hormone, antiserotonergics, antiadrenergics, ketogenic diet, and neurosurgical procedures. In the final chapter we consider the long-term outcome in this disorder and provide guidelines for the assessment of individual prognosis based upon diagnostic studies and response to therapy.

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Richard A. Hrachovy

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Chapter 1

Introduction: Overview and Definitions

1. OVERVIEW OF THE DISORDER

In this chapter, we briefly outline the major features of the disorder and identify some of the more controversial and as yet unresolved issues, including those of optimal therapy and basic underlying pathophysiology. In subsequent chapters, these topics will be explored in more detail.

1.1 History

Infantile spasms is a specific disorder that occurs in infancy and early childhood. The seizures have been recognized as an epileptic phenomenon since they were first described by William West in 1841, and consist of brief motor contractions that have been described in the literature by a very large number of terms in addition to infantile spasms, such as massive spasms, flexion spasms, jackknife seizures, infantile myoclonic seizures, blitz-krampfe, and salaam seizures. Approximately 100 years after the original description, Gibbs and Gibbs (1952) described a unique interictal EEG pattern, hypsarrhythmia, which occurs in a large number of these patients. Most patients with this disorder also have some degree of mental and developmental retardation, and the triad of epileptic spasms, retardation, and hypsarrhythmia has become known as West's syndrome. Over the past several decades, a considerable world literature pertaining to this disorder has accumulated. However, classifications and clinical descriptions of the seizures, based largely on routine bedside observations, have been highly variable, and this lack of uniformity has led to considerable confusion and controversy. Our understanding of the clinical

manifestations of this disorder was greatly increased by the development of long-term polygraphic/video monitoring techniques in the 1970s. These techniques also provided objective means of evaluating the acute effects of therapy on seizure frequency and the EEG.

1.2 Epidemiology

The overall incidence of this disorder is around 1 case per 3,225 live births (0.03%), although this figure varies considerably with geographic region. The lowest incidence is found in the United States, Great Britain and Korea, and the highest in Finland, Denmark and Sweden. The vast majority of cases begin during the first year of life (approximately 94%), and the peak onset age is 6 months. Most cases arise sporadically, and familial occurrence is relatively rare. While a male preponderance has been reported in most studies, with male-to-female ratios of 1.12-1.42 to 1, other studies have reported little or no sex difference.

1.3 Clinical manifestations

Motor spasms are the most frequent presenting manifestation of this disorder, and typically consist of brief, bilaterally symmetrical, contractions of the muscles of the neck, trunk, and extremities. The exact character of the spasm depends on whether the flexor or extensor muscles are predominantly affected, on the distribution of the muscle groups involved, and on the position of the body (e.g., supine versus sitting). The intensity of the spasm may vary from a massive contraction of all flexor muscles, resulting in a jackknife movement at the waist, to a minimal contraction of muscles such as the abdominal recti. Periods of attenuated responsiveness, which have been termed arrest phenomena, may occur following a motor spasm and may also occur independently. The spasms are often associated with other phenomena including eye deviation, rhythmic nystagmoid eye movements, and respiratory pauses. Alterations in heart rate occur rarely, and, while many infants cry following a spasm, crying does not occur as an ictal phenomenon. Although the spasms associated with this disorder may occur in an isolated fashion, around 70-80% occur in clusters, with the number of spasms per cluster varying from 2 to more than 100. Spasm rates of up to 13 per minute have been recorded, and the intensity of the motor contractions within a cluster usually waxes and then wanes.

Infantile spasms is associated with mental and developmental retardation in most cases (74-96%), and about 50% have major neurological deficits. Based on the history and diagnostic findings at the time of onset, patients can be divided into two main groups: cryptogenic or symptomatic. A patient is classified as cryptogenic if there is no abnormality on neurological examination, no known associated etiological factor, development has been normal prior to onset of the spasms, and the CT/MRI findings are normal prior to institution of therapy.

Utilizing these criteria, approximately 20% of patients currently are classified as cryptogenic, with the remaining patients being classified as symptomatic. The use of functional imaging techniques (e.g., positron emission tomography and single photon emission computed tomography) may further reduce the percentage of patients classified as cryptogenic. Classifying a patient as cryptogenic or symptomatic is crucial when considering long-term prognosis (see below).

Infantile spasms is a time-limited disorder, and epileptic spasms usually cease within a few years, even in cases that do not respond to initial therapy. However, most patients with this disorder continue to have significantly impaired mental function, and an evolution to other seizure types occurs frequently.

1.4 Electroencephalographic features

The interictal EEG pattern most commonly associated with infantile spasms is hypsarrhythmia, which is characterized by random high voltage slow waves and multifocal spikes which vary from time to time both in duration and location. Hypsarrhythmia is a highly dynamic pattern, with transient alterations in the pattern often occurring throughout the day. Also, several variants of the originally described pattern are now recognized. A variety of other interictal EEG patterns may occasionally be associated with this disorder, including diffuse slowing of the background activity, focal slowing, focal or multifocal spikes and sharp waves, and generalized slow spike and slow wave activity. In a small number of infants, the EEG background activity may appear normal.

A variety of ictal EEG patterns are associated with the motor spasms. These include a generalized slow-wave transient, generalized sharp-and-slow-wave transients, and attenuation episodes, occurring alone or with superimposed faster frequencies. These patterns may occur alone or in various combinations.

While abnormal evoked potentials have been reported in some studies (visual, auditory and somatosensory), this is not a consistent finding. Sleep characteristics are typically abnormal in infantile spasms, and often include a decreased total sleep time and low values for stage REM.

1.5 Neurodiagnostic imaging

While CT and MRI findings are normal in approximately one third of patients, the majority are abnormal and often demonstrate generalized or focal atrophy, and various congenital anomalies. In addition, MRI has been reported to reveal evidence of delayed myelination in some cases. Studies using PET and SPECT have reported changes in up to 97% of infantile spasm patients, and have included demonstration of both focal and diffuse areas of metabolic or perfusional dysfunction.

1.6 Differential diagnosis and related syndromes

The diagnosis of infantile spasms is sometimes delayed for weeks, or even months, because parents, and even physicians, do not recognize the motor phenomena as being seizures. Colic, Moro reflexes, and startle responses are diagnoses occasionally made by pediatricians. Also, observers may confuse the epileptic spasms with normal hypnagogic jerks (sleep starts) or rhythmic movements (head banging or rocking) occurring during drowsiness and sleep, and transient flexor-extensor posturing of trunk and extremities of nonepileptic origin.

Various non-epileptic medical conditions can also be confused with infantile spasms, including spasmus nutans, benign neonatal sleep myoclonus, and benign myoclonus of early infancy. EEG or combined EEG/video monitoring may be required in these cases to clarify the diagnosis.

A number of other epileptic syndromes seen in infancy and early childhood can present diagnostic difficulties, and can be confused with infantile spasms. Two of these, early infantile epileptic encephalopathy (Ohtahara syndrome) and early myoclonic encephalopathy, are closely related to infantile spasms, and differ primarily with respect to age of onset. Both of these entities may exhibit an evolution over time to infantile spasms. The Lennox-Gastaut syndrome is also closely related to infantile spasms and shares many characteristics with it, although it has a later age of onset. Since infantile spasms not infrequently evolves to Lennox-Gastaut syndrome, transitional forms are seen with characteristics common to both entities.

Other epileptic syndromes including benign myoclonic epilepsy in infancy, severe myoclonic epilepsy in infancy, and epilepsy with myoclonic-astatic seizures have ictal and EEG characteristics that permit clear differentiation from infantile spasms, although EEG/video monitoring is often required.

1.7 Relationship to other seizure types

Approximately 40-50% of patients with infantile spasms have other types of seizures at some time, either preceding the onset of spasms, concurrently with spasms, or after spasms have stopped. For example, seizures can occur in the neonatal period, and may resolve completely so that a seizure-free period exists for several weeks or months before the onset of epileptic spasms. In other cases, partial or generalized seizures may precede spasms only briefly, or may begin at some time after the onset of spasms. Such seizures may persist even after spasms have stopped, and in other cases appear for the first time long after spasms have ceased. Essentially any seizure type can be seen in patients with infantile spasms including generalized (tonic, tonic-clonic, atonic, myoclonic, and atypical absence), as well as partial forms. While other types of seizures are observed most frequently in symptomatic patients, they also occur in some cryptogenic cases.

The presence of these other seizure types in infantile spasms patients in most instances is thought to reflect the diversity of underlying pathology, and it is consistent with this view that in most cases epileptic spasms and other seizure types appear to occur independently of each other. However, in a small subset of infantile spasms patients it has been observed that spasms and partial seizures may occur in a coupled fashion, with, for example, a cluster of spasms regularly following a partial seizure, or partial seizures tending to occur during spasm clusters. This behavior has suggested to many investigators that under some circumstances spasms, presumably arising at a brainstem level, may be triggered by epileptogenic processes arising within focal cortical sites responsible for partial seizures.

1.8 Etiological factors

Approximately 80% of patients with infantile spasms can be classified as symptomatic based upon neurological and diagnostic imaging findings documented at the time of onset. Around 200 specific pre-, peri-, and postnatal factors have been implicated as possible etiological factors in this disorder. Prenatal factors include cerebral dysgenesis, intrauterine infection, hypoxia-ischemia, prematurity, and many genetic disorders. Perinatal factors include traumatic delivery and hypoxia-ischemia, while postnatal factors include head injury, CNS infection, hypoxia-ischemia, and intracranial hemorrhage. However, of the 200 potential etiological factors that have been identified, only 16 can, at this time, be clearly identified as having a true causal relationship with infantile spasms. For the others, the possibility of a chance, or coincidental, relationship has not been excluded.

While DPT immunization has often been suggested as an etiological factor for this disorder, statistical studies have demonstrated that the apparent association between DPT immunization and infantile spasms is coincidental and that no causal relationship exists.

1.9 Pathophysiology

The basic pathophysiology of infantile spasms is not known. Considerable evidence suggests that brainstem dysfunction may be involved and various investigators have suggested that altered neurotransmitter systems within this area may be responsible. These hypothetical models do not exclude the possibility that these critical brainstem region(s) may be affected by distant neuroanatomical sites, including the cortex, since the brainstem receives input from many other areas. Several other pathophysiological mechanisms have also been proposed. It has been suggested, for example, that infantile spasms may result from a failure or delay of normal developmental processes, or that it is the result of a defect in the immunological system. Finally, it has been suggested

that corticotropin-releasing hormone, a potent age-specific convulsant in the rodent, may play a mechanistic role in this disorder.

While no 'common denominator' has yet been discovered to explain the characteristics of this disorder, it is clear that groups of patients with this disorder differ significantly from normal subjects in many ways. In addition to the high incidence of specific structural brain abnormalities that have been associated with this disorder, there is a similarly diverse group of metabolic dysfunctions that have been identified in many patients, such as disturbances of monoamine pathways, amino acid abnormalities, and neuropeptide abnormalities. Further evidence for the frequent occurrence of metabolic disturbance in this disorder has recently been provided by improved neurodiagnostic techniques such as PET and SPECT. Finally, the role of genetic factors is still unclear, although several of the identified etiological conditions that have a definite causal relationship with infantile spasms have a genetic basis.

1.10 Treatment

Although numerous studies concerning the treatment of infantile spasms have been published, no consensus exists, nor has a true "standard of care" yet been established. While hormonal therapy (ACTH and corticosteroids) is currently the initial treatment of choice in most cases, because of various methodological problems, as well as the still incomplete understanding of the natural history of this disorder, several divergent opinions have evolved regarding the optimal application of this therapy. Some investigators consider ACTH and corticosteroids to be equipotent, whereas others consider ACTH to be superior. Furthermore, two specific approaches have evolved for treating infantile spasms with ACTH: Some physicians recommend using large doses of ACTH (40-160 U/day) and long durations of therapy (3-12 months), whereas others advocate low doses of ACTH (<1-40 U/day) for relatively brief periods (1-6 weeks). Some proponents of high-dose, long-duration therapy report better control of seizures and greater EEG improvement with such therapy compared with low-dose, short-duration therapy. However, other controlled studies have not supported this conclusion, and have indicated no significant difference in either response or relapse rates between the patients assigned to high-dose or low-dose ACTH therapy .

In addition to hormonal therapy, a number of other agents have been used to treat infantile spasms. Several of these, including vigabatrin, nitrazepam, valproate, pyridoxine (vitamin B_6), topiramate, zonisamide, immunoglobulin, and thyrotropin releasing hormone (TRH) have been demonstrated to have efficacy in at least some infantile spasms cases.

Surgical removal of specific brain lesions (e.g., neoplasms, cysts) has occasionally been reported as an effective form of treatment for infantile spasms. However, in recent years there has been a greater emphasis on the surgical treatment of patients without apparent anatomical lesions on traditional

neuroimaging , but who exhibit focal metabolic or perfusional abnormalities revealed by PET or SPECT. Although surgical treatment may abolish seizures in some of these patients, further controlled, prospective studies are needed to determine which patients may benefit from surgery, and if long-term development is significantly improved following surgical intervention.

The phenomenon of spontaneous remission in untreated patients is poorly understood, but of critical importance in assessing the efficacy of all treatment modalities. Available data indicate that spontaneous cessation of spasms and disappearance of the hypsarrhythmic EEG pattern can begin within one month of the onset of this disorder, and, that 25% of patients will experience spontaneous remission within one year of spasm onset. This phenomenon must always be considered when interpreting results of any therapeutic trial in this disorder, and must also be remembered in discussing possible pathophysiological mechanisms underlying infantile spasms.

1.11 Long-Term Outcome

The overall prognosis for unselected infantile spasms patients is poor. The average mortality rate is approximately 12% within the first few years following diagnosis, and only 16% of patients achieve normal mental development. Around half of the patients will continue to have seizures of some type indefinitely, while 17% will exhibit an evolution to the Lennox-Gastaut syndrome. Approximately 61% will have abnormal EEGs, and 44% will have persistent neurological deficits.

However, patients classified as cryptogenic by current criteria have a significantly more favorable prognosis. About half of these patients eventually achieve a normal mental status, in contrast to only around 6% of those classified as symptomatic. Similarly, seizure control can be expected in approximately 77% of cryptogenic subjects, compared to 46% of the symptomatic group. Mortality is also low in the cryptogenic group (approximately 3%).

Other favorable prognostic indicators are sustained response to therapy (i.e., without relapse), and an absence of other seizure types in addition to epileptic spasms. Some studies have suggested that a short treatment lag (the time elapsed between onset of the disorder and institution of therapy), an older age of onset, and the presence of a classical hypsarrhythmic pattern are also indicators of a more favorable outcome, but these findings do not currently have as much support as do the other factors.

It is still not known if any of the therapeutic measures used in this disorder actually result in an improvement of developmental outcome, mortality, or development of other seizure types.

2. DEFINITIONS

The classical description of West syndrome requires the presence of three diagnostic elements: infantile spasms, a hypsarrhythmic EEG pattern, and mental/developmental delay. This definition implies that the term "infantile spasms" encompasses only the particular motor behavior pattern that is unique to this disorder, and clearly separates it from the other two elements. Under this definition "infantile spasms" is simply used as a description of the seizure event, with no other implications, as was originally proposed by Gibbs, et al (1954). However, this usage has not been followed consistently in the medical literature, and, in fact, the term "infantile spasms" has more commonly been used synonymously with West syndrome. Under this latter usage, "infantile spasms" means a specific age-related medical condition associated with unique motor spasms, which is typically associated with hypsarrhythmia and developmental delay. The terminology is further confused by the fact that many investigators now accept a diagnosis of West syndrome if any two of the three classical elements are present.

Examination of the still current International League Against Epilepsy (ILAE) Classification of Epileptic Seizures (Commission, 1981) and the ILAE Classification of Epileptic Syndromes (Commission, 1989) does little to clarify the confusing terminology. First of all, the unique characteristics of the motor spasms associated with this disorder are not specifically recognized in the classification of epileptic seizures, and the only category in which these events reasonably fit is "myoclonic seizures". Second, while West syndrome is recognized in the classification of epileptic syndromes, where it is included as a type of generalized epilepsy, the definition in this document perpetuates the dichotomous use of the term "infantile spasms" by including it as a synonym for West syndrome, and also including it as one of the three primary characteristics of West syndrome. The ILAE definition also allows a diagnosis of West syndrome if one element of the classical triad is missing.

In spite of the inconsistent terminology associated with this disorder, we believe that the entity is itself actually very well defined, and usually may be clearly distinguished from other age-related disorders associated with myoclonic events. Consequently, in this monograph, we will use the terms "infantile spasms" and "West Syndrome" interchangeably to represent the clinical syndrome associated with the classic diagnostic triad: spasms of epileptic origin, a hypsarrhythmic EEG pattern, and mental/developmental delay. When referring specifically to the unique seizure events present in this disorder we will either use the unmodified term "spasms", which is consistent with the terminology suggested in the recent ILAE Proposed Diagnostic Scheme (Engel, 2001), or "epileptic spasms", which is consistent with the Semiological Seizure Classification scheme suggested by Luders, et al. (1998), and which more clearly differentiates these events from myoclonic activity of non-epileptic origin. We believe that it is possible to make an unambiguous diagnosis of infantile

spasms/West syndrome on the basis of only two of the three basic diagnostic criteria, i.e., epileptic spasms and the hypsarrhythmic EEG. However, it is much more difficult to justify such a classification in the case of an infant with developmental delay who subsequently develops epileptic spasms, but who does not exhibit hypsarrhythmia. As considered in more detail in chapter 7, full consideration of other factors may indicate another, more appropriate, diagnosis in such cases.

Chapter 2

History: 1841 - 1960

William J. West (1793-1848), a physician from Tunbridge, England, approximately 22 miles southeast of London, undoubtedly did not suspect that his name would eventually be linked with a devastating childhood neurological disorder. While his practice did involve children, he was best known for his pioneering work in the surgical management of ovarian cysts (West, 1837; Lux, 2001). His letter to the journal Lancet in early 1841, titled 'On a peculiar form of infantile convulsions' (West, 1841) was, thus, written not so much as a scientific work as it was a plea for help from the medical profession: "*As the only case I have witnessed is in my own child, I shall be very grateful to any member of the profession who can give me any information...*". His one year old son, James, the subject of the letter, had developed an unusual convulsive disorder at 4 months of age, characterized by "*...slight bobbings of the head forward...*" which over time "*...increased in frequency, and at length became so frequent and powerful, as to cause a complete heaving of the head forward towards his knees, and then immediately relaxing into the upright position, something similar to the attacks of emprosthotonus: these bowings and relaxings would be repeated alternately at intervals of a few seconds, and repeated from ten to twenty or more times at each attack, which attack would not continue more than two or three minutes; he sometimes has two, three, or more attacks in the day...*". Dr. West also described how his son had been normal and healthy at birth, and that his development had been normal until he was four months old, but that now he "*..neither possesses the intellectual vivacity or the power of moving his limbs, of a child of his age...*". This letter, constituting the first published description of infantile spasms known, was remarkable in that it provided a very succinct, yet complete description of the major features of the disorder as we now know it, with respect to the mode of onset, the character of the spasms, the phenomenon of clusters of spasms, the recognition that the

disorder has a convulsive basis, and the fact that it is associated with impairment of mental/neurological development.

In this original description of infantile spasms, Dr. West also pointed out two other aspects of the disorder that are still recognized today: its refractoriness to therapy and its rarity. With respect to treatment he stated "*I commenced an active treatment of leeches and cold applications to the head, repeated calomel purgatives, and the usual antiphlogistic treatment; the gums were lanced, and the child frequently put into warm baths. Notwithstanding a steady perseverance in this plan for three or four weeks, he got worse, the attacks being more numerous, to the amount of fifty or sixty in the course of a day. I then had recourse to sedatives, syrup of poppies, conium, and opium, without any relief...*". He also concluded that this disorder "*...may be a very rare and singular affection...*", after consulting with a number of his colleagues, including Drs. Clarke and Locock in London, who, between them, had seen only 6 similar cases in their extensive practices. According to Dr. West's report, the condition was called "salaam convulsion" by Dr. Clarke.

To our knowledge, no further reports of this condition appeared in the medical literature until 1849, when Newnham described 4 cases, including an expanded description of James West, made possible by additional information supplied by Mrs. West following the recent (1848) death of her husband, Dr. West. While Newnham's description of the disorder is generally in agreement with that of West's earlier report, several other important observations were documented for the first time. For example, he noted "*It is to be remarked that in each of the recorded cases, the severe attacks of the peculiar bowing have always been preceded by sleep; they have been always noticed to occur with especial severity in the morning after the night's sleep, or after the customary morning nap.*" He also recognized that other types of seizures could be associated with this disorder, noting that "*...it often passes into epilepsy, or some other form of infantile convulsions.*" Additionally, he made the important observation that the ictal events could in some cases involve extensor muscles, while in other cases they were flexor in character. Newnham also started a long tradition associated with this disorder by proposing a name change – in this instance from "salaam convulsion" (i.e., bowing or greeting seizure), as attributed to Clarke (West, 1841), to "eclampsia nutans" (i.e., nodding seizure).

Several authors have provided very comprehensive reviews of the early history of this disorder, including Gastaut and Poirier (1964), Jeavons and Bower (1964), Lacy and Penry (1976) and Fukuyama (2001). During the one hundred years between 1849 and 1949 relatively few reports were published (approximately 65 according to Gastaut and Poirer [1964]), and these, for the most part, described additional cases and provided confirmatory evidence for the major features of the disorder as described previously by West (1841) and Newnham (1849). Perhaps the most significant new feature described during this period was the recognition of the two major etiological categories - idiopathic (now usually called cryptogenic) and symptomatic - by Fere (1883),

although this important distinction was apparently not widely appreciated until much later (Zellweger, 1948). Zellweger also observed that this disorder was more common in males, reporting a male/female ratio of 1.6:1 in a total of 88 cases (26 from his series, and 62 from review of other published cases).

Much of the early literature is difficult to interpret, due both to the diversity of names used to describe the disorder (see below), and the fact that without EEG confirmation it was often difficult to differentiate true epileptic spasms from other, non-epileptic, motor events that may occur in children (Jeavons and Bower, 1964). However, it does seem clear that by 1950 the general characteristics of the disorder were clearly established and recognized by most investigators, a wide variety of etiological factors had been identified, and there was no effective therapy (Jeavons and Bower, 1964).

Interest in this disorder increased markedly after 1950, when several investigators reported associated EEG abnormalities. The first report describing the occurrence of any specific EEG pattern in association with the disorder now recognized as infantile spasms was apparently that of Lennox and Davis (1950). These investigators, in a study comparing the clinical correlates of the slow spike and wave pattern (petit mal variant, 2 Hz spike-wave) to those of the 3 Hz spike and wave pattern, reported that 37 (18.5%) of 200 patients with the slow variant had seizures characterized as "massive myoclonic jerks", which they equated with the "Blitz Krampf" type of seizure described in the German literature (they were not aware of the earlier descriptions of West or Newnham). While the descriptions of the seizures provided by Lennox and Davis are certainly consistent with infantile spasms, they did not provide any illustrations of the actual EEG patterns associated with these particular events (although they did show examples of slow spike-wave patterns associated with other seizure types). Thus, it is not clear if these patients had EEG patterns that would now be classified as slow spike and wave (and thus may have been more consistent with the Lennox-Gastaut syndrome), or whether they may have had patterns best classified as variants of *hypsarrhythmia.* In support of the latter possibility, Lennox and Davis, in their description of the slow variant pattern, state that it may be focal, appearing in only one lead, or lateralized, occurring in the leads from one side of the brain, and that the localization may be either constant or shifting, and that the morphology can be variable.

A year later, Vazquez and Turner (1951) presented 10 cases with a syndrome they designated "Epilepsia en flexion generalizida", and which, from their description, was entirely consistent with infantile spasms. They described an EEG pattern that was typically associated with this syndrome (seen in 8 of their 10 patients), as a diffuse, paroxysmal, cerebral dysrhythmia characteristic of "Petit Mal". However, examination of the sample tracings provided in this report suggests that in most instances the pattern would be consistent with hypsarrhythmia.

The most definitive description of the interictal EEG pattern commonly associated with infantile spasms was provided in 1952 by Gibbs and Gibbs as:

> *" ...random high voltage slow waves and spikes. These spikes vary from moment to moment, both in duration and location. At times they appear to be focal, and a few seconds later they seem to originate from multiple foci. Occasionally the spike discharge becomes generalized, but it never appears as a rhythmically repetitive and highly organized pattern that could be confused with a discharge of the petit mal or petit mal variant type. The abnormality is almost continuous, and in most cases it shows as clearly in the waking as in the sleeping record."*

Gibbs and Gibbs coined the term "hypsarhythmia" to designate this typical pattern (derived from the Greek words *hypsi* [high or lofty] and *arrhythmos* [unrhythmical]). While the original term was spelled with a single 'r', most recent authors have used the double 'r' form, 'hypsarrhythmia', as suggested by Jeavons and Bower (1964). Hypsarrhythmia has subsequently been widely recognized as the most characteristic EEG pattern associated with infantile spasms, particularly in its early stages, although it is now known that this feature is highly dynamic, and a number of variations are known (Hrachovy et al., 1984).

Several other reports appeared around this same time, providing additional information regarding the EEG characteristics of this disorder. Kellaway (1952) described 50 cases, and noted that while the basic EEG characteristic was a diffuse spike and wave pattern, there was wide variation in the configuration, and that lateralization, especially in the temporal regions, was not uncommon. Similarly, Gastaut and Remond (1952) described the associated EEG pattern as consisting of diffuse slow activity mixed with slow spike-wave complexes of variable distribution.

From the historical point of view, one of the most remarkable features of this disorder is the large number of names that have been proposed by various investigators over the years. While most current investigators use 'infantile spasms' (Gibbs and Gibbs, 1952) and/or 'West syndrome' (Gastaut et al., 1964) to designate this disorder, at least 76 other terms have been used by various investigators (Table 2.1), although it now seems likely that a significant number of patients included in some of these categories had other conditions that, especially in the absence of electroencephalography, were easily misclassified (Jeavons and Bower, 1964). This plethora of names has contributed significantly to the uncertainty that has arisen in the past regarding various clinical aspects of the syndrome and the efficacy of various therapeutic regimens, due to confusion with other medical conditions of both epileptic and nonepileptic character.

A major increase of interest in this disorder was precipitated by the report of Sorel and Dusaucy-Bauloye in 1958 that ACTH was an effective treatment, leading to prompt control of spasms in a number of cases, as well as improvement of mental status in some instances. Prior to this time, there had

Table 2.1 **Synonyms for Infantile spasms/West syndrome**

(Major sources: Gastaut et al, 1964; Lacy and Penry, 1976; Roger and Dulac, 1994; Fukuyama, 2001)

Acces spasmodiques
Akinetic seizures
Astatic seizures
Blitz krampfe
Blitz- und Grusskrampfe
Blitz, nick, und salaamkrampfe
Blitzkrampfe
Blitz-nick-salaam krampfe
Bosartige Blitz- und nickkrampfe
Bosartige nickkrampfe
Clonies du tronc
Commotions epileptiques
Crises symetro-toniques
Crises toniques anterieures
Crises toniques axorhizomeliques
Drop Seizures
Eclampsia nutans
Encephalite myoclonique du nourrisson
Encephalopathie de la premiere enfance avec dysrythmie majure
Encephalopathie myoclonique infantile avec hypsarythmie
Epilepsia en flexion generalizada
Epilepsia nutans
Epilepsie maligne symetrotonique du nourrisson
Epilepsie myoclonique grave de l'enfant
Epilepsie nutans
Epilepsie spasmodique infantile avec hypsarythmie
Flexion spasms
Generalized mass muscle jerks
Greeting spasms
Grusskrampfe
Head nodding
Hyperkinesies paroxystiques
Infantile massive spasms
Infantile myoclonic epilepsy
Infantile myoclonic jerks seizures)
Jack-knife convulsions (seizures)
Komplimentierkrampfe
Lightning fits
Lightning major spasms (seizures)

Table 2.1 (Continued)

Maladie des spasmes en flexion de la premiere enfance
Massive infantile spasms
Massive myoclonia
Massive myoclonic jerks
Massive spasms
Minor motor epilepsy (seizures)
Minor seizures
Minor startle seizures
Myoclonic petit mal
Myoclonic spasms of infancy
Myoclonies type B
Nickkrampfe
Nictitatio capitus
Nodding convulsions
Nutatio capitus
Pallidum epilepsie
Piccolo male propulsivo
Propulsions epileptiques
Propulsive seizures
Ruckkrampfe
Salaam spasms (convulsions)
Salaamkrampfe
Secousses epileptiques
Spasme nutant
Spasmes en flexion
Spasmes en flexion avec dysrythmie majure
Spasmes salutatories
Spasmus nictitans
Spasmus nutans
Startle seizures
Static seizures
Tento keiren
Tic d'assentiment
Tic de salaam
Tic d'inclination
Tics de reverence
Tique von salaam

been no effective treatment, although many agents, including numerous anticonvulsants, were commonly tried (Jeavons and Bower, 1964; Lacy and Penry, 1976). The study of Sorel and Dusaucy-Bauloye (1958) was followed by numerous other reports which confirmed the efficacy of ACTH (see Chapter 11,

and Appendix 2), although a long-term effect on mental/developmental status remains unproven (see Chapter 12).

There has been much speculation over the years regarding the basic etiology and pathogenesis of infantile spasms, but these aspects remain elusive (see Chapters 9 and 10). Newnham (1849) concluded "...that the injury done to the brain is progressive..." in this disorder, and speculated that the spinal cord was the first to be involved, followed by inflammatory action involving the medulla, and eventually deterioration of higher regions responsible for intellectual functions. Since that time there has been ample proof that central nervous system injury of any kind, pre-, peri- and post-natal, as well as various congenital malformations, may be etiological factors (Jeavons and Bower, 1964; Lacy and Penry 1976). Yet, there remain those cryptogenic cases in which no etiological factors are apparent, and development is normal until the time of onset.

Chapter 3

Epidemiology

1. INTRODUCTION

Epidemiology is a discipline concerned with the investigation of disease etiology, control, and distribution within the population, and the methods used are designed to extract meaningful relationships and correlations among multiple factors that may influence these basic parameters, and include a broad spectrum of experimental designs and biostatistical techniques. This chapter is more narrowly focused, and is primarily concerned with the demographics of infantile spasms, and considers its distribution within the population as a whole, as well as its frequency of occurrence within specific subpopulations. In addition, the familial and genetic aspects of the disorder are reviewed. Other epidemiological data pertaining to diagnostic characteristics, etiology, and effectiveness of therapy have been integrated into subsequent chapters, including Chapter 4 (Clinical manifestations), Chapter 9 (Etiological factors), Chapter 11 (Treatment), and Chapter 12 (Long-term outcome).

2. FREQUENCY OF OCCURRENCE

2.1 Age distribution

The age of onset of infantile spasms has been studied extensively, and it is well established that most cases begin during the first year of life, although it can begin as early as the first week of life, or as late as 3 years or longer (Fig. 3.1). Table 3.1 summarizes the findings from several representative studies that have provided specific information regarding the age distribution of this disorder within a variety of geographical locations. In the majority of these studies the average onset age was approximately 6 months, although several reported an

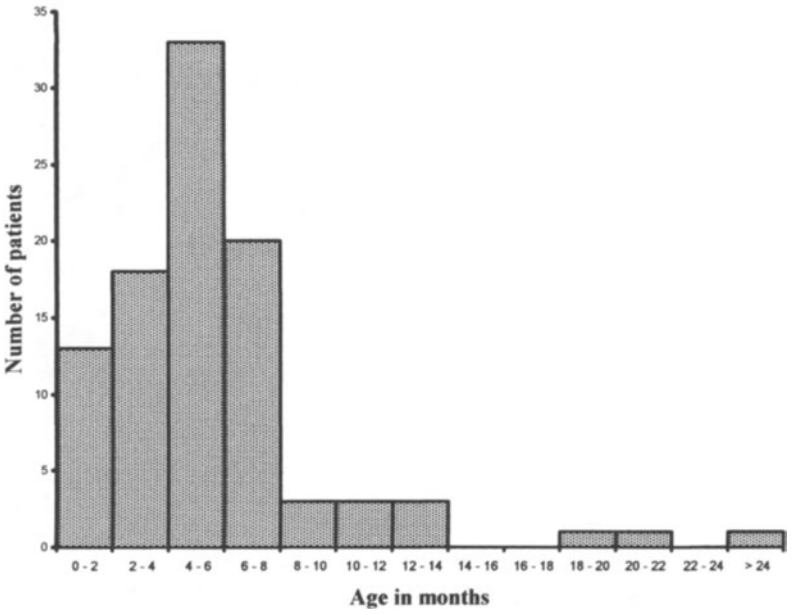

Figure 3.1 Age of onset of infantile spasms in 96 infants. Onset was during the first year in 94% of the cases. (Reprinted from *Pediatric Clinics of North America,* Vol. 36, Hrachovy, R.A. and Frost, J. D., Jr., Infantile Spasms. pp 311-329, copyright 1989, with permission from Elsevier Science)

average of 5 months, and two reported somewhat higher values of 7 and 10 months. No consistent geographical differences were apparent in these studies. Seven of the studies included in Table 3.1 also provided information regarding the proportion of cases that began beyond the age of 12 months. The observed range for this measure was 2 to 13%, with an overall average value of 6% for the seven studies. Consequently, it can be concluded that infantile spasms is most likely to occur at around 6 months of age, and only rarely begins after the age of one year.

2.2 Incidence

Infantile spasms has long been recognized as a rare disorder (West, 1841), although its exact frequency in various populations is still uncertain. The most commonly used epidemiological measure of the frequency of occurrence of a disorder is the incidence, which may be defined as the number of new cases of a particular disorder that occur within a specified time period, in a specific population (Timmreck, 1998). Incidence is, thus, a rate, or ratio, and its proper estimation consequently requires precise information regarding not only the

number of cases that occur in a particular geographical region, but also an accurate measure of the size of the general population itself. As has been pointed out previously (Cowan and Hudson, 1991; Hurst, 1994), relatively few studies of infantile spasms have been conducted which provide sound estimates of the incidence, and, within this limited group, the use of somewhat different definitions for both the population base, and the cases included often make precise comparisons difficult. One very basic problem concerns the current definition of infantile spasms as specified in the most recent Classification and Terminology of the International League Against Epilepsy (Commission, 1989) which states that it "...always occurs before the age of one year." As Hurst (1994) has emphasized, this definition has not been used in prior epidemiological studies, and in most instances it is not possible to derive corrected values from the information presented. However, since this restrictive definition is not generally accepted in clinical practice (primarily because it leaves undefined those otherwise clear-cut cases that begin after 12 months of age), we feel that it is reasonable to accept cases of any age, as long as the other diagnostic criteria are met (see Chapter 4).

Table 3.1 **Onset age of infantile spasms (months)**

	Time period	Country	Avg. age at onset	Onset age > 12 months
Bellman, 1983	1976-1979	Great Britain	5	4 %
Brna et al., 2001	1978-1998	Canada	6	
Chiemchanya et al., 2001	1997-1999	Thailand	6	
Howitz and Platz, 1978	1976	Denmark	6	
Hrachovy and Frost, 1989b	1976-1987	United States	6	6 %
Koul et al., 2001	1993-2000	Oman	6	2 %
Kramer et al., 1998	1975-1995	Israel	6	
Kurokawa et al., 1980	1975	Japan	6	13 %
Liou et al, 2001	1990-1997	Taiwan		4 %
Livingston et al., 1958	<1955	United States		10 %
Lombroso, 1983	1958-1976	United States	6	5 %
Mahdi et al., 1990	1982-1989	Saudi Arabia	5	
Matsumoto, 1981b	1963-1974	Japan	10	
Matsuo et al., 2001a,b	1989-1998	Japan	6	
Rantala and Putkonen, 1999	1976-1993		6	
Rantala et al., 1996	1967-1973	Denmark	5	
Sidenvall and Eeg-Olofsson, 1995	1987-1991	Sweden	6	
Suzuki, 2001	1995-2000	Japan	7	
Wong, 2001	1970-2000	Hong Kong	6	
Young, 2001	1998-1999	Taiwan	6	

Table 3.2 **Incidence of Infantile Spasms (per 1000 live births)**

Authors	Time period	Country	Incidence	Age range
Bobo et al., 1994	1987-1988	United States	0.05 *	0-24 mo
Bellman (NCES), 1983	1976-1979	Great Britain	0.13	2 - 36 mo
van den Berg and Yerushalmy, 1969	1960-1967	United States	0.16	0-5 yrs
Hwang, 2001	1997-1999	S. Korea	0.17	all children
Verity et al., 1992	1970-1980	Great Britain	0.20	0-10 yrs
Nelson, 1972	1959-1966	United States	0.26 **	0-12 mo
Trevathan et al, 1999	1975-1977	United States	0.29	0-24 mo
Luðvigsson et al., 1994	1981-1990	Iceland	0.30	all
Brna et al., 2001	1978-1998	Canada	0.31	all
Lee and Ong, 2001	1998-1999	Singapore	0.31	0-24 mo.
Matsuo et al., 2001a,b	1989-1998	Japan	0.31	all
Rantala and Putkonen, 1999	1976-1993	Finland	0.41	all
Riikonen, 1995	1960-1991	Finland	0.42	all
Sidenvall and Eeg-Olofsson, 1995	1987-1991	Sweden	0.45	all
Shields et al. 1988	1967-1973	Denmark	0.53 ***	0-24 mo
v. Wendt et al., 1985	1966-1980	Finland	0.60	0-14 yrs

* Calculated from Bobo et al. (1994) based on 11 incident cases.

** Value calculated by Hurst (1994) based on data of Nelson (1972)

*** Value calculated by Hurst (1994) based on data of Shields et al. (1988).

Table 3.2 summarizes the findings of 16 reports which either provide definitive incidence data for infantile spasms, or include sufficient quantitative data to permit its calculation with reasonable certainty. Most of these studies have used the number of live births occurring during the analysis period (within the specified geographical area) as the reference population (i.e., as the

denominator when calculating the incidence ratio), although an occasional study (e.g., Bobo et al., 1994) used actual counts of the referral population to provide essentially equivalent data. In order to facilitate comparison among the various studies, we have converted all reported incidence values to the equivalent number of cases per 1000 live births (e.g., if 43 cases were detected among 215,000 live births, this would be equivalent to 1 per 5000 live births, or 0.2 per 1000 live births).

As inspection of Table 3.2 reveals, there is considerable variability across studies with respect to both the time period (i.e., the number of years over which data were accumulated) and the age range for accepted cases of infantile spasms. In some studies (e.g., Lee and Ong, 2001) incidence data were based on observation periods of only 1-2 years, while in others (e.g., Brna, et al., 2001) data accumulated over many years were combined. However, assuming that no major changes in the basic incidence of this disorder took place over the past 30-40 years (see below), these differences do not appear to present significant problems in terms of ability to compare values across studies. On the other hand, the variability of the included age range across the studies might be expected to present a more significant problem. In some studies (e.g., Trevathan et al., 1999) only children less than one or two years of age were included, whereas in some other studies (e.g., Matsuo et al., 2001a,b) older children were also considered. While these different criteria for inclusion will certainly alter the observed incidence rates due to the fact that infantile spasms can occur in older children, the potential error is, fortunately, very small. As noted above (section 2.1), approximately 94% of infantile spasms cases begin before the age of one year. Consequently, the calculated incidence value is only slightly affected by including cases greater than one year (e.g., if the yearly incidence in a particular population of children in the 0-12 month age range is found to be 0.20 per 1000 live births, then it would be expected that the incidence would be no more than 0.21 per 1000 live births if all ages were included). Thus, in spite of some methodological differences among the studies included in Table 3.2, it seems likely that such differences have produced relatively small errors, and that it is reasonable to compare the results across studies.

The incidence values reported in the 16 studies included in Table 3.2 range from a low of 0.05 per 1000 live births (based on data from Bobo, et al., 1994) to a high value of 0.6 per 1000 live births (v. Wendt et al., 1985), with an average value of 0.31 per 1000 live births (or, equivalently, a range of 1 case per 1,667 live births to 1 case per 20,000 live births, with an average value of 1 case per 3,225 live births). This 10-fold difference in the reported incidence rates across studies is unlikely to be solely a result of the methodological issues discussed above. Other factors, such as random variation associated with relatively small numbers of cases in some instances, or inaccuracies in the estimations of the reference populations (i.e., the number of live births during the study period) may contribute to the observed wide range of values, although this can not be determined with certainty. However, the results of the studies conducted so far

strongly suggest that much of the observed variability is a reflection of the geographic location, a finding that could be a result of differential susceptibility of certain ethnic populations, or an environmental effect.

Based upon the currently available evidence, the lowest incidence of infantile spasms is observed in Great Britain (Bellman, 1983; Verity et al., 1992), South Korea (Hwang, 2001), and the United States (van den Berg and Yerushalmy, 1969; Nelson, 1972; Bobo et al., 1994; Trevathan et al. 1999), with values ranging from 0.05 to 0.29 cases per 1000 live births (or one case per 3,448 to 20,000 live births). Intermediate values were noted in Iceland (Luðvigsson et al., 1994), Canada (Brna et al., 2001), Singapore (Lee and Ong, 2001), and Japan (Matsuo et al., 2001a,b), with incidences of 0.30 to 0.31 cases per 1000 live births (or one case per 3266 to 3333 live births). The highest incidences have been observed in the Scandinavian countries of Finland (v. Wendt et al., 1985; Riikonen, 1995; Rantala and Putkonen, 1999), Sweden (Sidenvall and Eeg-Olofsson, 1995), and Denmark (Shields et al., 1988), with values ranging from 0.41 to 0.60 per 1000 live births (or one case per 1,667 to 2439 live births). This pattern suggests the possibility of a correlation of incidence with geographical latitude, with higher latitudes, in general, being associated with higher incidences of infantile spasms. It has been suggested that this pattern could be related to differences in solar radiation patterns (Cortez et al., 1997), and, in support of this hypothesis this group found that the number of new cases of infantile spasms peaked during the darkest months (Dec-Jan) in Toronto, Canada, a finding that could not be explained by a simple peak in the number of births. However, this finding was not confirmed in another Canadian study (Brna et al., 2001) which found no significant seasonal or temporal clustering of cases. Consequently, the reasons for the apparently unequal geographical distribution remain unclear.

One important issue that has only rarely been addressed using epidemiological techniques is the possibility of a long-term decrease in the frequency of this disorder due to factors such as improved pre-, peri- and postnatal medical care. This question has been addressed in only two studies, and the results in the two cases give very different results. In a study conducted in southern Finland, Riikonen (1995) found no significant difference in the overall incidence of infantile spasms for the time period extending from 1960 through 1976 (0.41 per 1000 live births, based on a total of 107 cases), as compared to the time period extending from 1977 through 1991 (0.43 per 1000 live births, based on a total of 102 cases). Thus, in spite of decreased perinatal mortality, and a decreased incidence of low birth weights among the identified cases during the more recent time period, the incidence of this disorder did not decline in this geographical region. On the other hand, the results of a study conducted by Brna et al. (2001) in Canada (Nova Scotia and Prince Edward Island) during a more recent time period do suggest a decreasing trend. The overall incidence of infantile spasms during the time period 1978-1991 was found to be 0.34 per 1000 live births, as compared to an incidence of only 0.16 per 1000 live births for the 1992-1998 time period (based on a total of 75

patients for the entire study period). These authors urge caution in the interpretation of the results due to the small number of subjects accrued per year, and the relatively large variability observed in the incidence values for individual years (ranging from a low of 0.09 per 1000 live births in 1979 to a maximum value of 0.59 per 1000 live births in 1983). Hughes and Tomasi (1985) have documented an apparent decline in the incidence of hypsarrhythmia in their laboratory (Chicago) from a peak in 1958 to a plateau around 1970. However, these findings are difficult to interpret since it is likely that significant changes in the referral patterns may have also occurred during that time as well. These investigators noted that the observed temporal incidence pattern of hypsarrhythmia resembled that of rubeola over the same time period, and suggested a possible etiological connection. In view of the above discrepant findings, it is clear that larger studies, conducted in various geographical regions, will be required to detect and quantify any long term changes in the incidence of this disorder.

2.3 Prevalence

Another epidemiological index of the frequency of occurrence of a disorder within a particular population is the prevalence. Prevalence is defined as the total number cases that are present within a defined population at a particular point in time (Timmreck, 1998), and is, thus, basically a "snapshot" of the cases present at some chosen instant (while incidence is concerned only with the number of new cases that occur during a specific time period, prevalence is a count of all active cases, both old and new). If the reference population chosen is restricted to young children, prevalence values for infantile spasms tend to be similar, but slightly lower, than incidence values due to the fact that while most cases have their onset during the first year of life, the proportion of cases declines in later childhood due to both mortality and remission or evolution to other seizure types (Cowan and Hudson, 1991). For example, Cowan and Hudson (1991) determined a prevalence of 0.25 per 1000 children if a 1-4 year age range was used. A lower prevalence (0.22 per 1000 children) was found if the population was restricted to children less than 1 year of age (presumably because some children had not yet developed the disorder), and a still lower value (0.19 per 1000 children) when the population was expanded to include all children up to 10 years of age (presumably due to mortality and remission or evolution). The other methodological problems noted above for incidence studies (section 2.2) apply to prevalence determinations as well.

There have been very few studies of the prevalence of infantile spasms. Table 3.3 summarizes the results of 7 investigations which have provided such information, or which include sufficient data to permit a reasonable estimation of the prevalence value. The average prevalence value for these studies is 0.25 per 1000 children, with a range of 0.14-0.52 per 1000 children. As with incidence, the wide range of reported prevalence values appears to be largely correlated

with geographical region. The lowest prevalences were observed in Japan (Ohtahara et al., 1981; Oka et al., 2001; Tsuboi, 1988) with values ranging from 0.14 to 0.18 per 1000 children. Intermediate values (0.20-0.25 per 1000 children) were recorded in Saudi Arabia (al-Rajeh et al., 1990) and the United States (Cowan et al., 1989), while the highest values (0.30-0.52 per 1000 children) were noted in Finland (Eriksson and Koivikko, 1997) and Denmark(Shields et al., 1988). As with the incidence, the cause (or causes) of this unequal geographical distribution remain to be determined.

Except for the information provided by comparison of studies in geographically distinct regions (Tables 3.2 and 3.3), there have been very few investigations of the racial aspects of this disorder. In an early description of the characteristics of infantile spasms patients, Druckman and Chao (1955) noted that the ratio of the numbers of white to black patients in their study (64:9) was the same as that of the clinic population as a whole, suggesting no significant difference in the risk element between these two groups. In more recent investigations, Cowan et al. (1989; Cowan and Hudson, 1991) reported that the prevalence was nearly twice as high in white children (0.21/1000 cases) as in black patients (0.12/1000 cases), but cautioned that these figures were based on small numbers of subjects, and could be influenced by many factors such as mortality differences, differential response to treatment, and evolution to other types of epilepsy. Lee and Ong (2001) determined the individual incidences of infantile spasms in Chinese (0.27 per 1000 cases), Malays (0.31 per 1000 cases) and Indians (0.33 per 1000 cases) living in Singapore, and suggested that due to the homogenous socio-economic and physical environment, differences in incidence would be best explained by genetic differences. However, these results must be considered as preliminary in view of the very small number of cases accrued during this study (total of 9 cases).

Table 3.3 **Prevalence of Infantile Spasms (per 1000 population)**

Authors	Time period	Country	Age	Prevalence
Ohtahara et al., 1981	1975	Japan	< 10 y.o.	0.14
Oka et al., 2001	1994	Japan	< 2 y.o.	0.16
Tsuboi, 1988	1975	Japan	3 y.o.	0.18
al-Rajeh et al., 1990	1984-1987	Saudi Arabia	all	0.20
Cowan et al., 1989	1983	United States	1-4 y.o.	0.25
Eriksson and Koivikko., 1997	1992	Finland	0-15 y.o.	0.30
Shields et al. 1988 (Hurst, 1994)	1967-1973	Denmark	0-2 yrs	0.52 *

* Value calculated by Hurst (1994) based on data of Shields et al. (1988).

Table 3.4 **Infantile spasms as a percentage of all epilepsy cases**

Based on consecutive hospital/clinic admissions:

Study	Country	—Epilepsy age group (%)— < 1 year	Children	All patients
al-Rajeh et al., 1990	Saudi Arabia	23	---	3
Berg et al., 1999	United States	---	4	---
Carabello et al., 1997	Argentina	47	---	---
Chiemchianya et al., 2001	Thailand	29	5	---
Doose and Sitepu, 1983	Germany	---	8	---
Druckman and Chao, 1955	United States	---	6	---
Kramer et al., 1998	Israel	47*	9*	---
Kurokawa et al., 1976	Japan	11**		
Livingston et al., 1958	United States	---	9	---
Loiseau et al., 1990	France	---	---	1***
Manonmani and Tan, 1999	Malaysia	---	---	3*
Matsumoto et al., 1983	Japan	31	---	---
Thambyayah, 2001	Malaysia	---	3	---
v. Wendt et al., 1985	Finland	---	3	---
Wong, 2001	Hong Kong	---	2	---

Based on prevalence of active cases in population:

Study	Country	—Epilepsy age group (%)— < 1 year	Children	All patients
Cowan et al., 1989	United States	5	2	---
Eriksson and Koivikko, 1997	Finland	---	8	---
Ohtahara et al., 1981	Japan	---	2	---

* Patients with neonatal seizures were not included in this study

** Includes all patients < 2 years of age

*** Includes all patients > 2months of age

2.4 Proportion of epilepsy cases

In spite of the relative rarity of infantile spasms, this condition comprises a significant proportion of the total number of cases diagnosed as epilepsy. Table 3.4 summarizes information from 18 studies that have determined the relative frequency of infantile spasms within the general population of individuals who have epilepsy (excluding cases with single or febrile seizures). Fifteen of these studies (shown in the upper portion of the table) were based on consecutive

clinic or hospital admissions for epilepsy accrued over a period of time, while the other three (shown in the lower part of Table 3.4) were based on determination of the prevalence of the various epilepsy types as determined within well-defined populations at a specific point in time. To facilitate comparison, the findings have been categorized into three age groups: '< 1 year' (including all children from birth to 12 months of age), 'Children' (including children of all ages, typically extending to 10 -15 years of age, but occasionally to 19 years), and 'All patients' (including both children and adults with epilepsy).

The reported proportions of infantile spasms cases among children with epilepsy in the 0 to 12 month age category are highly variable, ranging from as low as 5 % in a prevalence study conducted in the United States (Cowan et al., 1989) to as high as 47% in studies conducted in Argentina (Carabello et al., 1997) and Israel (Kramer et al., 1998). The reason for this high degree of variability across studies is not evident, but may reflect significant differences in referral patterns to the institutions involved, as well as sampling error due to relatively small numbers of cases in some studies.

Somewhat more consistent results are evident in the studies that included children of all ages, with infantile spasms cases comprising from 2% to 9% of these groups. Again, the variability is likely to reflect differences in referral patterns and the limited size of some groups. There does not appear to be any correlation of this measure with geographical region.

Three studies (al-Rajeh et al., 1990; Loiseau et al., 1990; Manonmani and Tan, 1999) looked at the proportion of infantile spasms among all cases of epilepsy, both children and adults. All reported relatively low values (1-3%), reflecting the fact that infantile spasms is age-dependent, and rarely persists beyond early childhood.

3. MALE/FEMALE RATIO

Many investigators have reported the sex ratio observed in their study populations of infantile spasms patients, and, while this measure has varied greatly across studies, most have found a male predominance. A representative sample of studies providing information regarding the sex distribution is summarized in Table 3.5.

In these studies the male/female ratio ranged from 0.47, indicating a 112% excess of females, to as high as 4.25, indicating a 325% excess of males. However, the majority of these studies do show a male predominance (ratios > 1). Much of the variability appears to be due to the relatively small numbers of cases in many of the studies, as illustrated in Fig. 3.2, which plots the male/female ratio versus the corresponding size of the study population. For example, 7 of the 8 studies reporting a male/female ratio greater than 1.5 had sample sizes of less than 60 cases, and all of those reporting a female excess had sample sizes of 80 or fewer patients. Five of the studies included in Table 3.5

Table 3.5 **Male to female ratio in infantile spasms**

Study	Number of cases	M/F ratio	
Juul-Jensen and Foldspang, 1983	16	0.47	
Koul et al., 2001	44	0.83	
Young, 2001	41	0.84	
Rantala et al., 1996	80	0.90	**
Druckman and Chao, 1955	73	0.92	
Liou et al., 2001	25	0.92	
Fleiszar et al., 1977	77	0.93	
Rantala and Putkonen, 1999	37	0.95	
Chiemchanya et al., 2001	31	1.07	
Fejerman et al., 2000	116	1.07	
Suzuki, 2001	54	1.08	
Howitz and Platz, 1978	21	1.10	
Wong, 2001	105	1.10	
Livingston et al., 1958	698	1.12	
Kurokawa et al., 1980	757	1.19	
Bellman et al., 1983 (NCES)	269	1.22	
Matsuo et al., 2001a,b	47	1.24	
Matsumoto, 1981b	256	1.33	
Riikonen and Donner, 1979	107	1.38	
Lombroso, 1983	286	1.40	
Brna et al., 2001	75	1.42	*
Cowan et al., 1989	23	1.56	
Doose and Sitepu, 1983	18	2.00	
Sidenvall and Eeg-Olofsson, 1995	57	2.00	
Jeavons et al., 1973	150	2.26	
Luðvigsson et al., 1994	13	3.33	
Mahdi et al., 1990	26	3.33	
Bobo et al., 1994	21	4.25	

* Not significant, since the male and female incidences were similar.

** Entire population ratio was 1.24/1 (M/F)

had more than 250 cases each, and in these studies the male/female ratio ranged from 1.12 to 1.42. Consequently, the majority of the available evidence suggests a slight male predominance in this disorder, based upon the proportion of cases diagnosed.

The significance of the observed male predominance is, however, unclear. Most of the studies that have provided information regarding the sex ratio are of the case-series type, based on consecutive hospital or clinic admissions, and

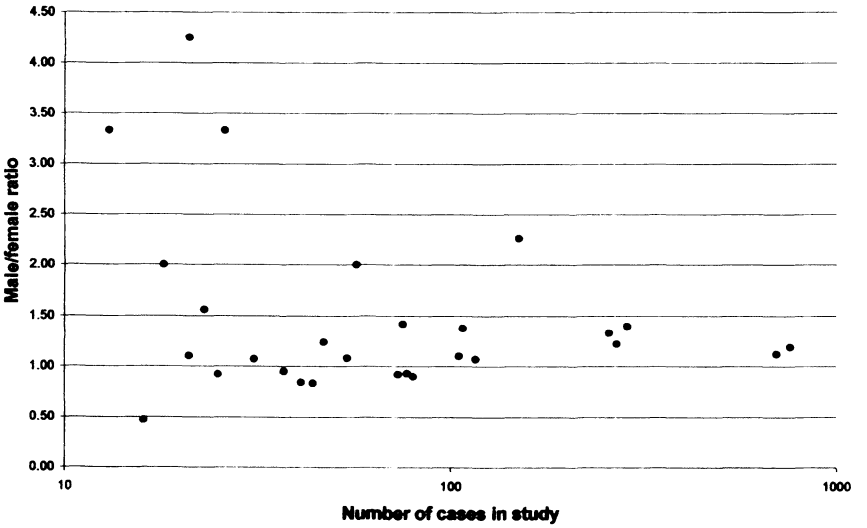

Figure 3.2 Relationship of observed male/female ratio to the size of the study population in 28 published studies of infantile spasms (see Table 3.5).

consequently no parallel information is available regarding the characteristics of the referral population as a whole. Thus, in most instances it is not known whether the male/female ratio in the referral population is 1.0, as assumed, or whether there actually might be more males (or females) in the particular population, in which case a male (or female) excess of infantile spasms cases would not be significant. In at least in one instance, this did appear to be the explanation. In the population-based study by Brna et al. (2001) the reported male/female ratio was 1.42, based on a sample size of 75 patients. The authors found, however, that the male predominance was not statistically significant, since the individual incidences of infantile spasms for males and females were very similar (presumably reflecting a higher male birth rate or lower male mortality in the overall population). One other study (Rantala et al., 1996) also documented a higher male/female ratio existing in the referral population (1.24:1), but, paradoxically, in this study the male/female ratio for infantile spasms patients was only 0.90, indicating a slight female excess.

In view of the above findings, it can only be concluded that while an excess of male cases is often observed in studies of infantile spasms, it is not always seen, and occasionally females predominate. In addition, the significance of observed unequal sex ratios is unclear, and in at least some instances, may simply reflect the characteristics of the referral population, rather than any pathophysiological feature of the disorder itself.

Table 3.6 **Family history of epilepsy in infantile spasms patients**

Study	Number of cases	Positive family history (%) Any epilepsy	Infantile spasms	I.S. in sibling
Kurokawa et al., 1980	757	1	0.5	---
Lombroso, 1983	286	5	---	---
Howitz, 1980	253	---	---	4
Gibbs et al., 1954	237	7	---	---
Jeavons and Bower, 1964	112	7	3	3
Rantala et al., 1996	80	4***	---	---
Fleiszar et al., 1977	77	---	4*	3*
Druckman and Chao, 1955	73	33	---	---
Millichap et al., 1962	61	15	---	---
Sidenvall and Eeg-Olofsson, 1995	57	9	0	0
Hoefer et al., 1963	40	---	---	5
Crowther, 1964	36	14	---	---
Watanabe et al., 1973	32	---	---	6
Trojaborg and Plum, 1960	30	20	7	7
Liou et al., 2001	25	0**	0	0
Luðvigsson et al., 1994	13	23	--	0

* None of 77 control children had a family history of infantile spasms

** 2.2% of 138 normal control subjects had a positive family history of epilepsy

*** 0.4% of a comparison group of 262 children with CNS infections had a positive family history of epilepsy

4. GENETIC/FAMILIAL FEATURES

A number of investigators have provided information regarding the familial characteristics of infantile spasms. Table 3.6 summarizes the findings of 16 studies in which the proportion of cases having a family history of epilepsy was determined. The percentage of cases having a positive family history for epilepsy of any type varies widely across studies, from a low value of 0% (Liou et al., 2001) to a high of 33% (Druckman and Chao, 1955). When only studies involving more than 100 patients are included (Gibbs et al., 1954; Jeavons and Bower, 1964; Kurokawa et al., 1980; Lombroso, 1983) the range is much lower (1 to 7 %), suggesting that at least some of the variability is due to sampling errors associated with small populations. However, methodological differences related to ascertainment of the historical information probably contribute to the differences as well. Interpretation of these data is further complicated by the fact that most studies did not provide control information indicating the family

history of epilepsy to be expected in normal subjects, or patients with other medical conditions, when evaluated with the same protocol. Such information was provided in only two studies, and they obtained somewhat conflicting results. In the study by Liou et al. (2001), none of the 25 patients with infantile spasms had a family history of epilepsy, whereas 2.2% of a control group including 138 normal children did have a positive history. On the other hand, Rantala et al. (1996) found that 4% of their 80 infantile spasms cases had a positive family history for epilepsy, in contrast to only 0.4% of a comparison group with CNS infections. In a related type of investigation, Fleiszar et al. (1977) did not find an increase of epilepsy in first or second degree relatives of children with infantile spasms, in comparison to relatives of a control group of children without infantile spasms (although there was a statistically significant increase in 3rd degree relatives of the patients, which the authors speculated might be a result of differential recall by the parents of children with infantile spasms). Consequently, in view of the divergent nature of the currently available information, it is not possible to conclude that a family history of epilepsy is significantly more common in children with infantile spasms.

Information regarding the familial occurrence of infantile spasms itself is also provided in Table 3.6. Six studies determined the number of cases with any family members who also had infantile spasms, with values ranging from 0% (Sidenvall and Eeg-Olofsson, 1995; Liou et al., 2001) to 7% (Trogaborg and Plum, 1960). Nine studies determined the number of cases who had siblings with infantile spasms, with the results ranging from 0% (Luðvigsson et al., 1994; Sidenvall and Eeg-Olofsson, 1995; Liou et al., 2001) to 7% (Trogaborg and Plum, 1960). Only one of these studies (Fleiszar et al., 1977) included a control group of normal children (total of 77), and none of these subjects had a family history of infantile spasms. In a nationwide survey conducted in Japan (Sugai et al., 2001), 34 familial cases of infantile spasms were detected. These occurred within 15 families (9 with 21 cryptogenic cases, and 6 with 13 symptomatic cases), with a maximum of 5 cases occurring in two generations of one family. Etiologies were the same within each family, and included cryptogenic (21 cases), Smith-Lemli-Opitz syndrome (2 cases), early delay (2 cases), Leigh syndrome (2 cases), X-linked (3 cases), and progressive encephalopathy with edema, hypsarrhythmia and optic atrophy (PEHO syndrome) (4 cases). Howitz (1980) studied 9 families in Denmark, each with 2 or 3 affected siblings (total of 19 cases with infantile spasms). Eight cases were determined to be symptomatic and 11 cryptogenic, and, unlike the study of Sugai et al. (2001), in some instances symptomatic and cryptogenic cases occurred in the same family. Consequently, the available information indicates that infantile spasms can be familial, and can involve cases with known etiological factors (see Chapter 9) as well as those classified as cryptogenic. The possibility that some of these cases occurred on chance basis must also be considered, although the design of the above studies did not permit this to be determined quantitatively.

Liou et al. (2001) reported that patients with infantile spasms were significantly more likely to have a positive family history of psychiatric disease than were normal children (12% and 4.3%, respectively). However, an earlier study by Fleiszar et al. (1977) found no significant increase of mental illness in relatives of infantile spasm patients, as compared to the relatives of control subjects.

5. SUMMARY AND SYNTHESIS

Approximately 94% of infantile spasms cases begin during the first year of life, and in nearly all cases the onset occurs prior to three years of age. Most studies have reported the average, or peak, onset time to be around 6 months of age. The average incidence of infantile spasms is approximately 0.31 case per 1000 live births (1 case per 3,225 live births), although a much wider range has been reported in studies conducted around the world (from 0.05 per 1000 live births, to 0.60 per 1000 live births). The lowest incidences have been recorded in the United States, Great Britain, and Korea while the highest rates occur in Finland, Denmark, and Sweden. While, in general, the highest rates have been associated with higher geographical latitudes, it is not known to what degree this represents an environmental influence (e.g., solar radiation patterns) as has been suggested by some studies, or variable susceptibility within different ethnic or racial groups as suggested by other investigations. It is also not clear whether or not the incidence of this disorder has remained stable over the past 40-50 years as some studies have indicated, or has declined as suggested by others.

The prevalence of infantile spasms (i.e., the total number of active cases at a particular time) is around 0.25 per 1000 children in the population at large, with a range of 0.14 to 0.52 per 1000 children. Like incidence, the prevalence values generally correlate with geographical region, and the highest values have been observed in Denmark and Finland. While a few studies, involving relatively small numbers of patients, have reported racial differences in the prevalence or incidence of infantile spasms within specific geographical regions, the available data do not provide unambiguous evidence for genetic differences in susceptibility.

Although infantile spasms is a rare disorder, it does account for a very significant fraction of the total number of children with epilepsy, with estimates ranging from 2 to 9% in several studies. Most studies have reported a male preponderance of infantile spasms, with male/female ratios of 1.12 to 1.42 noted in the larger studies. However, this figure is highly variable, and some studies have found no male/female difference, or have occasionally observed an excess of females. It is currently not clear if the preponderance of males in most studies represents an increased male susceptibility, or, as suggested in a few studies, simply reflects a larger proportion of male patients in the referral populations.

Specific information regarding the genetic aspects of infantile spasms is sparse, and much of the available evidence is highly variable. Many studies have

determined the proportion of cases having a family history of epilepsy of any type, with values ranging from 0% to as high as 33%, but most have not provided comparative data for normal subjects. It can only be concluded that a definitely increased family history has not been adequately proven in this disorder. On the other hand, the familial occurrence of infantile spasms clearly has been documented in a number of families, with etiologies involving both definite neurological syndromes with a genetic basis, as well as multiple cases with a cryptogenic classification (see Chapter 9).

6. FUTURE RESEARCH

There is clearly a need for additional well-designed epidemiological studies of this disorder. The majority of studies reviewed above have been case series, in which variable numbers of consecutively accrued patients are accumulated, and analyzed with respect to specific features. Such studies do not provide the basis for determining the significance of many aspects of the disorder, since characteristics of the general referral population are typically unknown. Consequently, more population-based and/or case-controlled studies which do provide the basis for determining the significance of the findings should be performed.

One specific area in which more definitive studies are required is the underlying basis for the observed geographical distribution of the incidence and prevalence of this disorder. Many investigators have documented the higher frequency of infantile spasms in certain regions such as Finland, Denmark and Sweden, but essentially nothing is known regarding the cause of this distribution. Environmental factors, such as differing patterns of solar radiation have been suggested, but, so far, have not been conclusively determined. Ethnic factors affecting susceptibility have also been proposed, but have not yet been well-studied in any sub-population. A better understanding of the factors involved would be expected to contribute to a more complete understanding of the pathophysiology of this disorder, and possibly lead to methods of prevention.

Definitive studies are also needed to determine if the incidence of infantile spasms is decreasing over time, as indicated in some studies, or has remained relatively constant as others have suggested. It would be particularly important to relate any detected changes in incidence patterns to concurrent changes in prenatal, perinatal, and postnatal medical care in the specific geographical regions studied.

While some familial cases of infantile spasms can be explained by the occurrence of known, inheritable, neurological disorders, many others involve cryptogenic cases. Consequently studies are needed in which a variety of epidemiological and genetic techniques are used to seek the underlying basis for these occurrences and to clearly differentiate them from cases which may occasionally occur on a chance basis. Such information is crucial to the eventual

determination of the undoubtedly multiple pathological factors underlying this disorder.

Finally, well-designed epidemiological studies should be performed to resolve the long-standing controversy regarding the male/female ratio observed in this disorder. If there truly is a preponderance of male cases, even if only in some populations, such information could provide clues which would be of potential value in understanding the genetic aspects of the disorder.

Chapter 4

Clinical Manifestations

1. INTRODUCTION

This chapter is concerned with the outward, or clinical, manifestations of infantile spasms and the natural course of the disorder over time. While many descriptions of the clinical features have been presented in the medical literature over the past 160 years, the details have varied considerably, and this has led to confusion regarding the precise characteristics of the disorder and the criteria for diagnosis (Lacy and Penry, 1976). The fundamental difficulty underlying this problem is the very brief duration of the typical ictal event associated with the disorder, coupled with its complex, and often variable, motor and behavioral manifestations. The often fleeting character of the spasms, together with their diverse and changeable configurations, usually precludes an accurate description by family members, as well as physicians, with the result that early diagnosis is not always achieved, and often the manifestations initially are attributed to other conditions, such as colic or startles. These characterization difficulties made it impossible for early investigators to accurately describe the behavioral features of the ictal events, and to clearly differentiate them from both normal infantile movements and other pathological conditions. Fortunately, technological developments such as time-synchronized polygraphic/video recording techniques have significantly improved our ability to precisely characterize the manifestations of this disorder over the past 25 years, and this, in turn, has resulted in a more definitive understanding of the range and features of the ictal events.

2. MODE OF ONSET AND NATURAL COURSE

As detailed in Chapter 3 (section 2.1), this disorder usually begins within the first year of life, and almost always prior to 3 years of age, with a peak onset at around 6 months. Quantitative information regarding the mode of onset is sparse

since the disorder may initially be subtle in its manifestations, and is often not recognized as a seizure disorder in its early stages (Rail, 1963; Bellman, 1983; Watanabe et al., 2001; Trevathan, 2002). Also, the behavioral aspects of the ictal episodes, even when clear-cut from the onset, are often confused with other events considered to be benign. For example, in the National Childhood Encephalopathy Study (NCES) conducted in Great Britain (Bellman, 1983) the child's mother had reported concern regarding twitching or jerking movements of the limbs to a physician in 79% of the cases eventually determined to be infantile spasms. However, in only 28% of the cases did the original physician diagnose the problem as a seizure disorder, and the correct diagnosis of infantile spasms was made at that time in only 11% of the cases. In a number of early studies of this disorder it was found that parents often initially attribute the spasms and other behavioral manifestations, such as crying, to pain associated with colic (Druckman and Chao, 1955; Chao et al., 1957; Bower and Jeavons, 1959). In the NCES study colic was thought to be the problem in 11% of the cases by the mother, and in 15% of cases by the child's physician. In other cases the spasms may initially be confused with startle responses (Moro reflex), which can also lead to delay in diagnosis (Bower and Jeavons, 1959; Jeavons and Bower, 1964; Lacy and Penry, 1976). These issues are discussed in more detail in Chapter 7.

While abnormal appearing motor activity (i.e., spasms) is the most frequently recognized initial manifestation of this disorder, regression of mental and/or motor abilities often occurs simultaneously (Illingsworth, 1955; Jeavons and Bowers, 1964). This is most apparent in the cryptogenic group, who exhibit normal developmental milestones until spasm onset, although further regression may also sometimes be observed in symptomatic patients who have manifested some degree of retardation since birth (Jeavons and Bower, 1964; Guzzetta et al., 2002). Guzzetta et al. (1993) have emphasized that the acute phase of infantile spasms may be characterized by fluctuations in performance, arousal and attention and disturbances of social and affective behavior rather than cognitive or operative skills. The developmental characteristics associated with this disorder are considered in more detail below (section 4).

Infantile spasms is a time-limited disorder, with spasms usually ceasing after a few years, even when treatment is not successful. Trojaborg and Plum (1960) reported that spasms usually disappear by 3-4 years of age, although a few cases persisted beyond that time. Jeavons and Bower (1960) reported a steady decrease over time in the number of patients still having spasms, and after 3 years (from onset) more than 50% were spasm-free. In a study of children not treated with hormonal drugs, we determined a spontaneous remission rate of 25% within one year of onset (Hrachovy et al., 1991). However, as detailed in Chapter 12, most patients continue to have significant developmental/mental delay, which is often severe, evolution to other seizure types is common, and the mortality rate is approximately 12%.

3. DESCRIPTION OF SPASMS

3.1 Role of EEG/polygraphic-video monitoring

The outwardly visible, or behavioral, manifestations of the cerebral epileptogenic processes associated with West syndrome can assume a wide variety of forms, with much variability observed both across patients, and from time-to-time within the same patient. The typical ictal event has been characterized as an epileptic spasm (Luders et al., 1998), defined as a muscular contraction of variable duration affecting predominantly axial muscles. However, the intensity of motor activation as well as the pattern of involved muscles, varies greatly, ranging from episodes characterized only by arrest of ongoing behavior (i.e., akinesia) to massive flexion of the body and extremities, and with durations ranging from less than one second (myoclonic jerks) to many seconds (tonic spasms and arrest events). These events can occur sporadically, in an isolated fashion, or serially, as clusters, with many events occurring per minute. In addition to spasms, a number of other transient phenomena have been identified as possible ictal events in this disorder, including autonomic changes, smiling, laughing, grimacing and crying. This complex picture, with high variability in terms of configuration, intensity, and temporal characteristics, usually precludes an accurate description of the ictal events in the home or routine clinical setting, and contributes to the sometimes conflicting descriptions in the medical literature. These problems, in turn, lead to delays in diagnosis and difficulties in determining the response to therapy.

Recognition of these problems related to the characterization of seizures and other phenomena associated with infantile spasms eventually led to the development of effective monitoring systems capable of providing precise information regarding the ictal events and their relationship to associated EEG activity. A schematic diagram of an early system devised for this purpose is illustrated in Fig. 4.1, and illustrates the multiple physiological parameters recorded over prolonged periods of time that are necessary to make the required correlations (Frost et al., 1978). This configuration provided simultaneous recordings of multiple EEG channels, eye movement (EOG), 7 electromyographic channels (EMG), respiration, electrocardiogram, galvanic skin response (GSR), and limb motion (triaxial accelerometers). Behavioral characteristics were monitored concurrently, and in a time-synchronized fashion, through the use of audio and video recording. A major advantage of this approach is the ability to replay questionable events repeatedly, either in real time, slow-motion, or accelerated time in order to precisely determine the time relationships among various parameters. Similar systems are now in widespread use, and permit the behavioral, motor and autonomic aspects of infantile spasms to be characterized and differentiated from non-ictal events. In addition, this approach has provided a much clearer picture of the typical features encountered in this disorder, as outlined in the following sections.

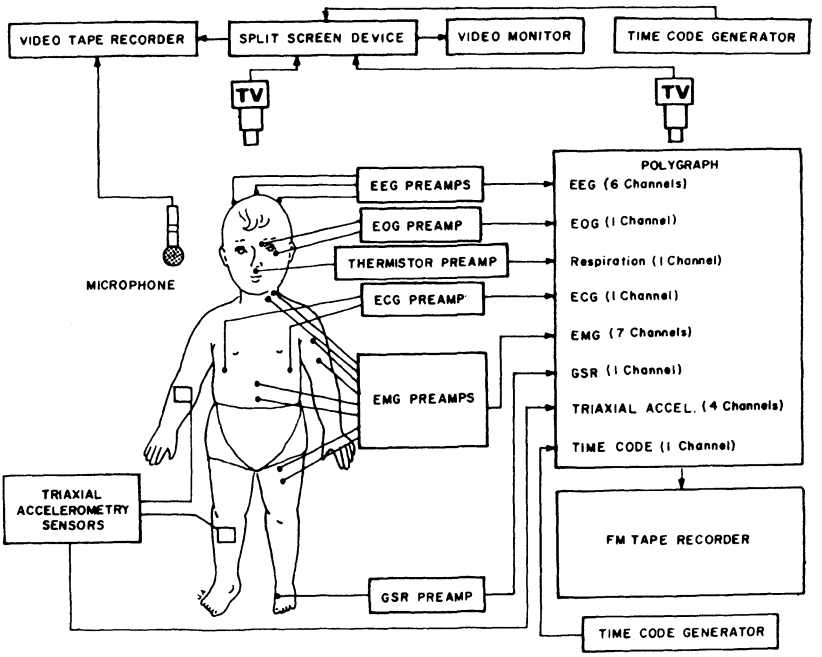

Figure 4.1 Schematic diagram of EEG/polygraphic/video monitoring system (Reprinted from *Epilepsia*, Vol. 19, Frost, J. D., Jr., Hrachovy, R. A., Kellaway, P., Zion, T. Quantitative analysis and characterization of infantile spasms. Pages 273-282, copyright 1978, with permission from Blackwell Publishing.)

3.2 Duration, intensity, muscular involvement, arrest

Prior to the advent of polygraphic/video monitoring many investigators did provide descriptions of the spasms, including West (1841), whose characterization was remarkably accurate (see Chapter 2). Most early descriptions emphasized the flexor character of the spasms (Kellaway, 1952; Livingston, et al. 1958; Baird, 1959; Pauli, et al., 1960), noting involvement of both the trunk and extremities. However, it was also recognized that the character of the spasms was quite variable, and the presence of extensor and/or mixed types was well documented (Newnham, 1849; Druckman and Chao, 1955; Chao, et al., 1957; Bower and Jeavons, 1959; Kellaway, 1959; Hoefer, et al., 1963; Jeavons and Bower, 1964).

In 1979, Kellaway et al. (1979) provided the first quantitative analysis of the characteristics of infantile spasms through the use of a time-synchronized video and polygraphic recording system. In this study, more than 5,000 ictal events, recorded from 24 patients with infantile spasms, were individually analyzed and grouped, according to the predominant features, as flexor, extensor, mixed, arrest, or asymmetrical spasms (Table 4.1). The muscle activity typically consisted of two phases: an initial phasic component with a duration not exceeding 2 seconds, and a subsequent tonic contraction lasting from 2-10 seconds (Fig. 4.2A), although this latter component could be absent (Fig. 4.2B). The typical flexor spasm (which accounted for 34% of the events) was associated with flexion of the trunk, neck, arms and legs, and, when sufficiently intense, resulted in the classical picture as described by West (1841) with the head moving rapidly toward the knees, and the torso "jacknifing" at the waist. The upper arms were either adducted (producing a hugging motion) or abducted (moving upward to either side of the head), while the lower arms were flexed at the elbow. Less intense flexor spasms could be manifested as head bobs with involvement only of neck muscles, shrugs involving primarily the shoulders, or brief contractions of the rectus abdominis musculature. Extensor spasms (making up 23% of the total) were characterized by abrupt extension of the neck and trunk, with extensor abduction or adduction of the arms and/or legs. The most common type of spasm (42% of the total) included both extensor and flexor components in variable patterns. Most frequently this consisted of flexion of the neck, trunk, and arms and extension of the legs, although other variations were documented. Asymmetrical spasms (1% of total) were recorded in one infant who characteristically maintained an abnormal posture. Episodes of attenuated responsiveness and akinesia sometimes followed the other types of spasms, and this phenomenon was termed "arrest". This type of event sometimes occurred independently, as the only evident ictal manifestation, in 3 patients, and accounted for 1% of the total number of seizures. Arrest episodes lasting as long as 90 seconds were recorded. As indicated in Table 4.1, many of the infants had

Table 4.1 **Distribution by type of 5,042 ictal events occurring in 24 patients with infantile spasms***

Seizure type	Number of Seizures (%)	Number of patients (%)
Mixed	2,117 (42 %)	22 (92 %)
Flexor	1,708 (34 %)	16 (67 %)
Extensor	1,136 (23 %)	12 (50 %)
Arrest	52 (1 %)	3 (13 %)
Asymmetrical	29 (1 %)	1 (4 %)

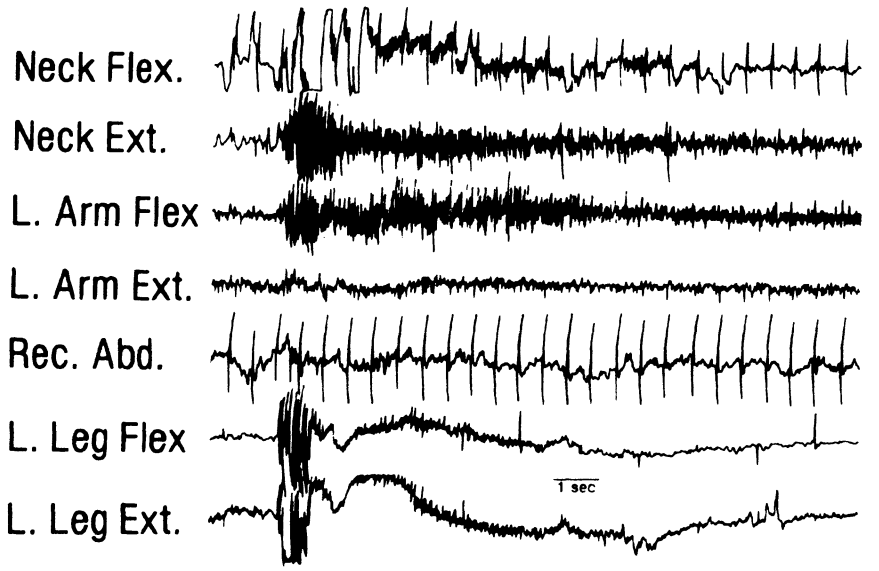

Figure 4.2A EMG activity associated with a single spasm, consisting of an initial phasic component lasting approximately 1 sec, followed by a lower amplitude tonic contraction persisting for several seconds. Tracings include recordings of EMG activity from the flexor and extensor musculature of the neck, left arm, and left leg, as well as the rectus abdominis.

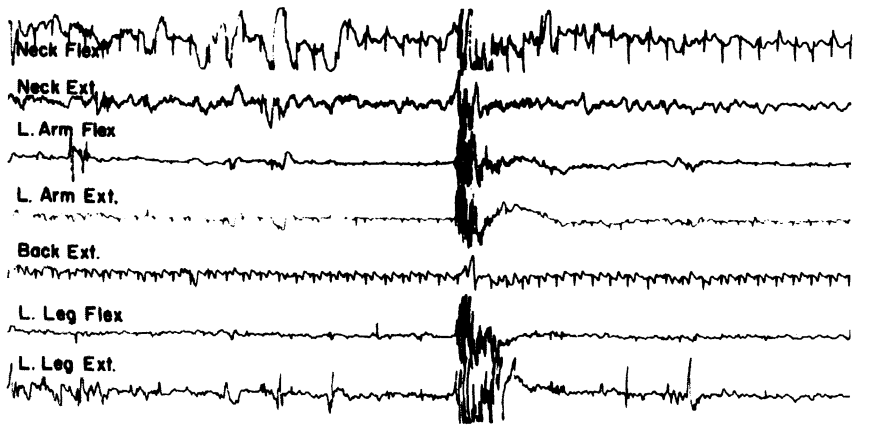

Figure 4.2B EMG activity associated with a single spasm, consisting only of a phasic component lasting approximately 1 sec. Tracings include recordings of EMG activity from the flexor and extensor musculature of the neck, left arm, and left leg, as well as the back extensors.

more than one of these seizure types, with 92% having at least some mixed spasms. The most common grouping was the occurrence of both flexor and mixed seizures, which was observed in 9 of the 24 subjects (38%). Mixed seizures alone were documented in 3 patients (13%).

In a later study, also making use of polygraphic/video monitoring, King et al. (1985) found similar results in a group of 10 patients experiencing a total of 1079 spasms. Durations of the initial (myoclonic) phase were reported to be less than one second, while the subsequent tonic phase could persist for up to 10 seconds. Arrest episodes as long as 28 seconds were documented. Flexor and mixed events were most common (42% and 39%, respectively), followed by extensor spasms (16%), and arrest episodes (3%). As in the study of Kellaway et al. (1979), more than one type of spasm typically occurred in the same patient, with all 10 patients exhibiting flexor and mixed events at some time during the monitoring period.

While most of the spasms in this disorder are bilaterally symmetrical in character (in terms of the degree of muscular activation), asymmetrical and unilateral events were occasionally reported even by early investigators (see Jeavons and Bower, 1964). However, the frequency of such events has varied markedly across those studies in which quantitative information was provided. For example, Kellaway et al. (1979) found asymmetrical spasms in only 1 of 24 patients (4%), while King et al. (1985) reported these events to occur consistently in 4 of their 10 cases (40%), and with variable lateralization in 5 other cases (50%), with 90% of the entire group exhibiting asymmetrical spasms at some time. Intermediate values have been reported by a number of other investigators (13% in Jeavons and Bower, 1964; 6% by Lombroso, 1983; 22% by Fusco and Vigevano, 1993; 14% by Haga et al., 1995a; 52% by Gaily et al., 1995; 9% by Gaily et al., 2001). While the basis for this wide range of observed values can not be determined with certainty, it is likely that it depends on multiple factors including sampling errors associated with the small number of subjects in the individual studies, different age ranges, body positioning and, most importantly, the lack of a standard basis for judging a spasm as asymmetrical. Thus, in some of the studies (e.g., Kellaway et al., 1979), no attempt was made to identify minimal asymmetries in the muscular activation pattern, whereas in other studies (e.g., King et al., 1985 and Gaily et al., 1995) the investigators specifically evaluated each spasm for such differences (although quantitative criteria were not indicated). In addition to this asymmetry pattern, a temporal asynchrony of muscular activation has been described by several investigators, in which the onset of contraction in the musculature of one side of the body is slightly delayed with respect to the other side (Trojaborg and Plum, 1960; Gailey et al., 1995, 2001).

Based upon the above information it is clear that the ictal events associated with this disorder can assume a wide variety of patterns across patients, and also can sometimes vary greatly over time in terms of intensity and configuration even within an individual patient. The significance of the various patterns

(flexor, extensor, mixed, arrest) and of their variability in some patients is not clear at this time. At least a portion of the variability observed in individual patients is related to postural effects. For example, Livingston (1974) reported the character of the spasms could be altered significantly by changing the position of the patient from recumbent to sitting. Similarly, Vigevano et al. (2001) state that if the trunk is vertical the spasms are predominantly flexor, while if the patient is horizontal the seizures are largely extensor. However, this can not be the entire explanation since spasms are often observed to alter their characteristics over time while the patient remains in the same position. The type of spasms (flexor, extensor, or mixed) that occur in a particular patient do not appear to provide useful diagnostic or prognostic information, and the patterns do not differ significantly between cryptogenic and symptomatic groups (Lombroso, 1983; Haga et al., 1995a). On the other hand, asymmetric (and asynchronous) spasms have been found to occur much more frequently (and, in some studies, exclusively) in symptomatic patients, and, thus, are suggestive of an unfavorable outcome (Jeavons and Bower, 1964; Fusco and Vigevano, 1993; Gailey et al., 1995, 2001; Haga et al., 1995a).

3.3 Associated phenomena

A number of phenomena, in addition to muscular spasms and akinetic episodes, have been reported to occur in association with the seizures of infantile spasms, both as part of the ictal events and in the immediate post-ictal period (Table 4.2). Eye movements, including deviation alone or in association with rhythmic nystagmoid activity, were observed to accompany spasms in many early investigations of this disorder (Vasquez and Turner, 1951; Chao et al., 1957; Bower and Jeavons, 1959). These events are relatively common, and were observed in 55% of the spasms analyzed by Kellaway et al. (1979), and in 44% of the patients studied by Lombroso (1983). Several investigators have reported that eye deviation is confined to symptomatic cases, and, thus, is an indicator of poor outcome (Haga et al., 1995a; Vigevano et al., 1993). Other reported ocular manifestations of the ictal event include eye opening or closing (King, et al., 1985), pupillary dilatation (Druckman and Chao, 1955; Chao et al, 1957; Bellman, 1983), and lacrimation (Bellman, 1983).

Alterations of the respiratory rate were observed in 59% of the seizures in the series reported by Kellaway, et al. (1979). Similar changes were described by Lombroso (1983) in 54% of his series and in 60% of the patients studied by King et al. (1985). Other reported respiratory events include sighing and gasping (King et al., 1985) and hiccups (Bellman, 1983). Crying has often been observed in close association with spasms (Druckman and Chao, 1955; Chao et al., 1957; Livingston et al., 1958; Baird, 1959;Trojaborg and Plum, 1960; Rail, 1963; Hoefer et al., 1963; Jeavons and Bower, 1964; Anandam, 1983), but there is now general agreement, based upon polygraphic/video monitoring, that this is a postictal phenomenon and does not occur during the spasm itself (Kellaway et

Table 4.2 **Phenomena reported to occur in association with ictal events in infantile spasms**

Ocular events	Grunting noise*
Eye deviation*	Smile
Nystagmoid motion*	Grimace
Eye opening or closing*	Tongue/mouth movements*
Pupillary dilatation	Autonomic alterations
Lacrimation	Heart rate changes*
Respiratory rate alteration*	Pallor
Hiccups	Cyanosis
Crying	Sweating
After seizure*	Flushing
During seizure	Decreased responsiveness*
Laughter	Partial seizures*

al., 1979; Lombroso, 1983; King et al., 1985). It seems likely that this represents a response to the ictal events, such as fright, as suggested much earlier by Bower and Jeavons (1959). Laughter has also been described as occurring during some spasms (Druckman and Chao, 1955; Chao et al., 1957; Livingston et al., 1958; Matsumoto et al., 1981a; Bellman, 1983; Anandam, 1983), but it apparently has not been documented during polygraphic/video monitoring. In the study by King et al. (1985), 2 patients were found to make grunting noises during some of the monitored spasms.

Various facial movements may also be associated with the ictal event (Trojaborg and Plum, 1960; Druckman and Chao, 1955; Matsumoto et al., 1981a). Lombroso (1983) reported that 35% of the patients in his study sometimes exhibited grimacing or smiling during spasms. Similarly, King et al. (1985), documented various mouth and/or tongue movements in association with spasms in 60% of their patients.

A number of investigators have identified apparent alterations in autonomic nervous system function occurring in association with the ictal event, as manifested by signs such as heart rate changes, pallor, cyanosis, flushing, and sweating (Druckman and Chao, 1955; Chao et al., 1957; Bellman, 1983). Lombroso (1983) reported that flushing occurred during some spasms in 17% of his patients, and alterations of heart rate were found in 0.6% of the 5,042 spasms in the study by Kellaway et al. (1979).

A decreased responsiveness to external stimuli has been observed during some ictal events in this disorder (Druckman and Chao, 1955; Lombroso, 1983), and particularly during the longer tonic phases or during the arrest episodes (Kellaway et al., 1979). However, there have apparently been no specific and objective investigations of this phenomenon.

Partial seizures are known to sometimes occur in a time-locked (or coupled) relationship to the ictal spasms, and this aspect is discussed in detail in Chapter 8.

3.4 Temporal distribution

The tendency for the ictal events of infantile spasms to occur in clusters, or series, separated by longer seizure free periods has been recognized throughout the history of the disorder, and was summarized clearly by West (1841) in his original description of the disorder (see Chapter 2). While this characteristic has been confirmed by essentially all subsequent investigators, there have been surprisingly few quantitative investigations of the phenomenon. Based upon the use of polygraphic/video monitoring of 5,042 ictal events, Kellaway et al. (1979) found that at least some spasms occurred in clusters (two or more spasms in succession, separated by less than 60 seconds) in 21 of 24 patients (88%), and that 78% of all seizures occurred in this manner. As many as 125 spasms were observed in a single cluster, and a maximum spasm frequency of 13 per minute was documented. Also, it was noted that both the intensity and the frequency of occurrence of the spasms within a cluster would often gradually increase over time, and then decline until the cluster ended. These basic characteristics have, in part, been confirmed in several subsequent studies. Kurokawa et al. (1980) reported that clusters occurred in 75% of their 757 cases, while Gaily et al. (2001) observed this phenomenon in 84% of 44 cases. Plouin et al., (1993) reported that 70% of the 654 spasms recorded in their 67 patients occurred in clusters, and King et al. (1985) found that 47% of the 1079 spasms they recorded in 10 patients were within clusters. Viani et al. (1994b) reported cluster durations of 2-10 minutes, and found an average of 24 spasms per cluster. Thus, it is clear that the majority of patients have at least some spasms in clusters, but isolated ictal events are also common, and may be the exclusive mode of presentation in a few patients. The significance of this temporal distribution pattern remains unknown. Vigevano et al. (2001) found that the number of spasms per cluster and the spasm frequency did not differ significantly between symptomatic and cryptogenic cases. Similarly, Matsumoto et al. (1981a) reported that the proportion of cases with clusters did not differ significantly among various etiological categories.

Monitoring studies (Hrachovy and Frost, 1986) have also indicated that while the frequency of spasms usually is similar in consecutive 24-hour periods, marked variation of frequency can be observed when the recordings occur at 2-week intervals (see Fig. 11.3, Chapter 11).

3.5 Precipitating factors

Newnham (1849) was the first to describe a relationship between the frequency of the ictal events and sleep, noting that in all of his cases the attacks were more severe following awakening from nocturnal sleep, or following the morning nap. The subsequent literature concerning this issue is inconsistent, with some investigators confirming awakening as the most common precipitating factor (Druckman and Chao, 1955), while others maintained that they were more

frequent immediately prior to sleep onset, as well as upon awakening from sleep (Taylor, 1952; Baird, 1959; Jeavons and Bower, 1964), or even just after falling asleep (Anandam, 1983). However, studies that have investigated this relationship using objective techniques in which the sleep-wake status could be determined with certainty have confirmed Newnham's observations, and indicate that spasms occur only rarely during sleep. Using polygraphic/video monitoring, Kellaway et al. (1979) found that clusters of spasms were more frequent soon after arousal from sleep, and that there was no increase in the seizure incidence prior to or immediately after falling asleep. In this study it was determined that only 2.5% of the total number of spasms occurred while the patients were actually asleep. These infants did, however, have frequent awakenings during the night during which seizures occurred, and, as a result, the number of seizures that occurred at night (55%) was similar to the number recorded during the day (45%). An example of the time distribution of infantile spasms over a 24-hour period is provided in Fig. 4.3, and illustrates the occurrence of sporadic clusters of spasms during periods of wakefulness during both day and night time periods (Hrachovy and Frost, 1986). In another study using monitoring techniques, King et al. (1985) also found a relative increase of spasms soon after awakening, and a low number of spasms occurring during sleep (14%). The spasms that did occur during sleep in this study were all of the isolated type with no clusters. The low incidence of spasms during sleep has been confirmed in several other studies (Plouin, et al., 1987; Ohtsuka et al., 1993; Horita, 2001). However, clusters of subclinical ictal EEG discharges (i.e., not associated with muscular spasms) can occur during REM sleep and may be associated with eye movements (Iwase and Watanabe 1972; Horita et al., 1977; Horita 2001). These events may exhibit a transition to typical clinical spasms if the patient awakens from REM sleep during the cluster (Hrachovy et al., 1984).

Numerous other factors have been reported to precipitate seizures in this disorder, including loud noise, handling, feeding, infection, excitement, fright, anger, fever, hunger, need for urination or defecation, and excessive environmental heat (Taylor, 1952; Druckman and Chao, 1955; Chao et al., 1957; Baird, 1959; Anandam, 1983). These reports were largely anecdotal, and in the absence of careful controls it is difficult to establish a true causal relationship, as opposed to coincidental occurrences. Kellaway et al. (1979) were not able to confirm any of the above factors in their study based on polygraphic/video monitoring, and also noted the ineffectiveness of photic stimulation. However, in subsequent studies in larger numbers of patients, using polygraphic/video monitoring, we have on rare occasions documented cases in which typical spasms could be elicited reliably by unexpected loud noises or tactile stimulation (unpublished observations).

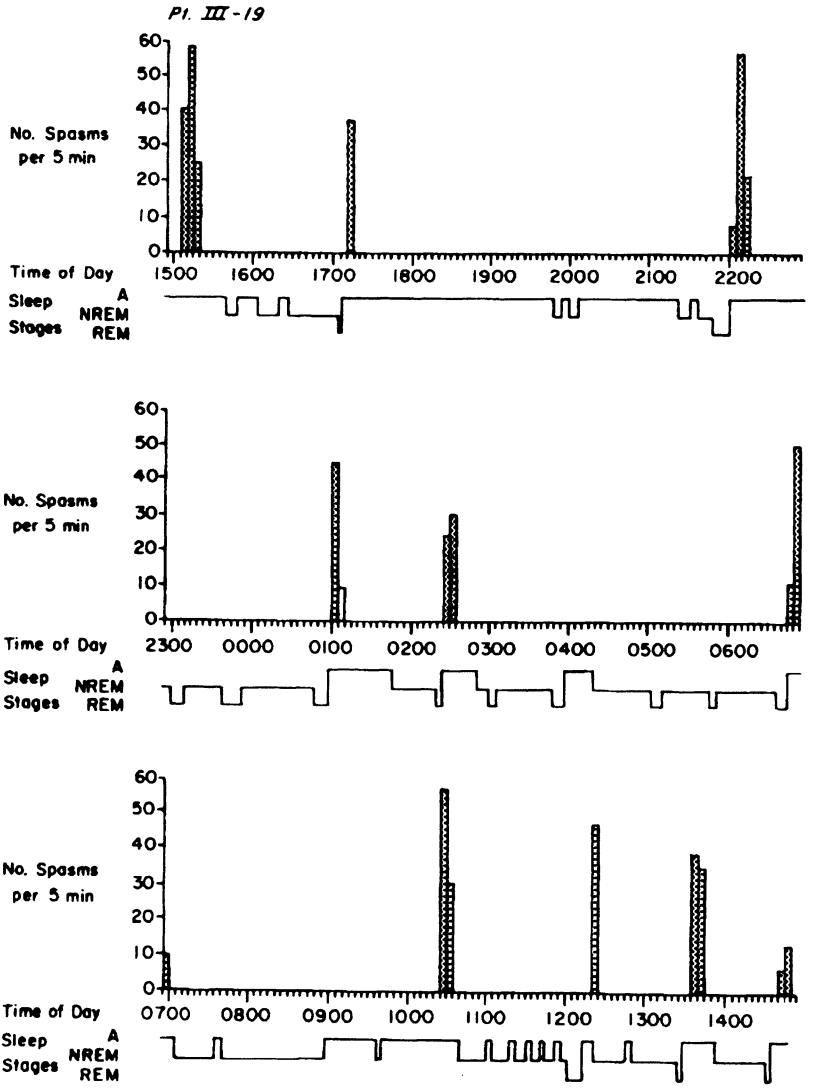

Figure 4.3 Temporal distribution of spasms over a 24-hour period. A, awake; NREM, non-REM sleep; REM, REM sleep. (Reprinted from *Intractable Epilepsy*, Schmidt, D. and Morselli, P. L., Eds. Hrachovy, R. A. and Frost, J. D., Jr. Intensive monitoring of infantile spasms. Pages 87-97, copyright 1986, with permission from Lippincott Williams & Wilkins)

4. DEVELOPMENTAL/NEUROLOGICAL ASPECTS

Some of the presenting characteristics of this aspect of the disorder were discussed above (section 2), and it was noted that the majority of patients with infantile spasms/West syndrome are developmentally delayed, usually with respect to both mental and motor skills. The number of patients exhibiting mental retardation ranged from 74% to 96% in several studies (Gibbs et al., 1954; Livingston et al., 1958; Bower and Jeavons, 1959; Kellaway, 1959; Kurokawa et al., 1980; Feng et al., 1991). While most investigators have not reported motor deficits independently, Gibbs et al. (1954) gave a value of 63% of the 237 patients in their series, and Livingston et al. (1958) reported a value of 50%. The manner in which developmental delay manifests is, however, variable, as is the degree of retardation, across patients. When this disorder occurs in children who have, until onset, exhibited normal development since birth, there is typically an arrest of further mental/motor development, and often a loss, or regression, of previously attained milestones (Illingsworth, 1955; Jeavons and Bowers, 1964), although this does not invariably occur. The developmental regression often appears to be related to the occurrence of the hypsarrhythmic EEG pattern rather than the onset of the epileptic spasms per se (personal observations). On the other hand, many children in the symptomatic category (i.e., with known pre-, peri-, or postnatal etiological factors) will have been developmentally delayed prior to onset of spasms, and often since birth. In these cases, particularly if the degree of retardation is severe, there may be no further decline in abilities following onset of infantile spasms. But, in cases in which the preexisting delay was of mild to moderate degree, additional regression can occur following infantile spasm onset (Jeavons and Bower, 1964). The number of children who exhibit developmental impairment prior to the onset of infantile spasms has ranged from 52% to 86% in several studies (Livingston et al., 1958; Anandam, 1983; Guzzetta et al., 1993; Koul et al., 2001).

Other neurological abnormalities are common in symptomatic patients, and primarily reflect the underlying etiological processes, and psychiatric manifestations may also be present in both symptomatic and cryptogenic patients (see Chapters 9 and 12). Visual and/or auditory impairment have been reported to be common in infantile spasms (Gibbs et al., 1954; Livingston et al., 1958; Hoefer et al., 1963; Rail, 1963; Feng et al., 1991; Castano et al., 2000; Koul et al., 2001). Specific deficits in visual attention (as evaluated through a test of the child's ability to shift the visual fixation point) have been reported by Guzzetta et al. (2002) preceding the onset of infantile spasms, with significant worsening of performance during the acute phase. Ocular abnormalities, revealed by ophthalmological examination, are also relatively common and occurred in 23% of the subjects studied by Hoyt (1979), and in 36% of those examined by Curatolo et al. (1981), and often established a specific etiological diagnosis.

The long-term outcome is poor in most infantile spasms cases, with a mortality rate of approximately 12%, and only around 16% of patients ever achieve normal development (see Chapter 12).

5. SUMMARY AND SYNTHESIS

Infantile spasms is a disorder of early childhood, typically beginning during the first year of life and almost always before the age of three years. It is usually characterized by the occurrence of brief, usually bilaterally symmetrical, motor spasms involving musculature of the trunk, neck, and limbs. Motor involvement is highly variable, both with respect to the intensity and the pattern of activation, and most spasms consist of both flexor and extensor components. Periods of behavioral arrest and unresponsiveness sometimes occur following a spasm, and can also occur independently. The ictal events can occur in an isolated fashion, but most frequently occur in clusters, during which the intensity of the spasms may wax and then wane. Developmental arrest typically occurs simultaneously with spasm onset in patients with previously normal development, and may worsen in those patients with preexisting delay. Neurological abnormalities are common, and often reflect underlying etiological factors. This disorder is time-limited, with spasms usually ceasing within a few years, whether or not treatment has been successful. However, an evolution to other seizure types is common, and most patients do not achieve normal mental function.

6. FUTURE RESEARCH

More specific information is needed regarding the developmental deficits (both cognitive and motor) that occur in the course of this disorder. In particular, the character of the developmental arrest that is often observed in children who have exhibited normal mental and motor progress up to the time of spasm onset should be better delineated and compared to that of children who have shown significant delay since birth. Such information could provide clues regarding the basic pathophysiology of this disorder by delineating the particular sensory, motor and cognitive parameters that deteriorate first and/or ultimately exhibit the greatest degree of impairment. Such studies would be of most value if information could also be acquired at two or more time points prior to the time of spasm onset in order to determine if the process underlying this disorder has a gradual development, or if, as most studies now suggest, begins simultaneously with the onset of epileptic spasms.

Chapter 5

Electroencephalography, Evoked Potentials, and Sleep

1. INTRODUCTION

Electroencephalography (EEG) is currently the only laboratory test that provides specific information useful for diagnosing infantile spasms. The interictal EEG is nearly always abnormal, and the most characteristic pattern, hypsarrhythmia, is almost exclusively associated with this disorder. While other diagnostic procedures, including hematological and biochemical determinations, as well as imaging techniques (CT, MRI, PET and SPECT), are often abnormal in patients with infantile spasms, they reflect underlying conditions and/or structural abnormalities which may be contributing etiological factors, but which are not specific for this disorder, or invariably present. The ictal EEG provides additional essential information regarding the nature of observed clinical events, and is required for confirming the epileptogenic character of spasms and other ictal phenomena, and differentiating them from non-epileptic events.

The emphasis in this chapter is on the diagnostic and prognostic utility of electroencephalography in infantile spasms. The interictal characteristics seen during the course of the disorder are described, as are the electrographic patterns that occur in association with the clinical spasms and other ictal events. Evoked potential characteristics are also considered in terms of potential diagnostic utility. The alterations of sleep characteristics seen in association with this disorder (as defined by EEG/polygraphic techniques) are considered, as are state-related changes in the characteristic ictal and interictal EEG patterns. Additional information regarding the use of electroencephalography in infantile spasms is provided in subsequent chapters dealing with differential diagnosis (Chapter 7), associated seizure types (Chapter 8), etiology (Chapter 9), pathophysiology (Chapter 10), treatment (Chapter 11), and outcome (Chapter 12).

2. INTERICTAL EEG PATTERNS

2.1 Hypsarrhythmia and its variants

Original definition As discussed in Chapter 2, in the early 1950s a number of investigators described the EEG characteristics associated with infantile spasms (Lennox and Davis, 1950; Vasquez and Turner, 1951; Gibbs and Gibbs, 1952; Kellaway, 1952; Gastaut and Remond, 1952). Gibbs and Gibbs (1952) called the interictal pattern which they believed to be most typical of this disorder 'hypsarhythmia', and this basic pattern subsequently has been confirmed as the most unique EEG feature of infantile spasms. Gibbs and Gibbs specified several defining characteristics of this pattern: 1) It is essentially continuous, 2) It is usually present both awake and asleep, 3) It consists of random high voltage slow waves and spikes, 4) The spikes vary in both location and duration, at times appearing focal, and at other times multifocal, and 5) Occasionally the spike discharges become generalized, but they never occur in a rhythmic and highly organized pattern such as petit mal or petit mal variant. In a subsequent publication (Gibbs et al., 1954), it is added that the chaotic appearance of this abnormality gives the impression of nearly total disorganization of cortical voltage regulation. Although it is not explicit in the original text (see Chapter 2), hypsarrhythmia has generally been considered to be characterized by a high degree of asynchrony between hemispheres with respect to both the spike/sharp wave activity and the high amplitude slow waves, as well as by a generally disorganized character of the background activity (Druckman and Chao, 1955; Trojaborg and Plum, 1960; Jeavons and Bower, 1964).

Frequency of occurrence It is difficult to determine with certainty the frequency with which this prototypical form of hypsarrhythmia occurs in infantile spasms. Gibbs and Gibbs (1952) reported only that it was common in infants with a history of spasms. They did comment that the diffuse spike activity characteristic of hypsarrhythmia tends to decrease with increasing age, and that it could be absent while the patient was awake, but present during sleep. They used the term "modified hypsarrhythmia" to describe an example in which the waking record was characterized by high voltage slow activity in all areas with a complete absence of spikes, although a more typical pattern persisted during sleep. Because the original description was not quantitative, subsequent investigators used somewhat differing criteria, with some adhering as rigidly as possible to the basic description (sometimes excluding patients not meeting the original description of hypsarrhythmia), while others adopted more inclusive rules. Thus, Druckman and Chao (1955), in a study of 73 patients who by clinical criteria were diagnosed as infantile spasms, found that only 38% had EEG findings entirely consistent with hypsarrhythmia. An additional 16% were classified as 'modified hypsarrhythmia', due to an increased degree of synchrony of the high voltage slow activity and the presence of some relatively normal

Table 5.1 **Frequency of hypsarrhythmia in infantile spasms (percent of patients exhibiting pattern)**

	Classical hypsarrhythmia	Modified hypsarrhythmia	Other EEG abnormality	Normal
Druckman and Chao (1955)	**38 %**	**16 %**	**37 %**	**8 %**
Jeavons and Bower (1964)	**47 %**	**19 %**	**33 %**	**1 %**
Anadam (1983)	**7 %**	**64 %**	**22 %**	**7 %**
Jacobi and Neirich (1992) *	**75 %**	**25 %**	**0 %**	**0 %**
Vacca et al. (1992)	**67 %**	**33 %**	**0 %**	**0 %**
Kholin et al. (2002)	**17 %**	**73 %**	**6 %**	**4 %**
Alva-Moncayo (2002) **	**9 %**	**91 %**	**----**	**----**

*** cryptogenic patients only** **** only patients with hypsarrhythmia included in study**

activity during wakefulness. Other abnormal, but non-hypsarrhythmic, EEG patterns were present in 37% of these children, and 8% of the EEGs were thought to be normal. Several other studies have provided similar information and, as illustrated in Table 5.1, the results are highly variable, with values reported for classical hypsarrhythmia ranging from 7 to 67 % of the patients, and those for modified hypsarrhythmia from 16 to 91%. This inconsistency is most likely a result of the lack of established standards delineating the criteria for modified hypsarrhythmia and the fact that the interictal pattern is often variable, and can exhibit different characteristics both within a given record and over long periods of time (see Section 2.2 below).

Variants of hypsarrhythmia In an initial attempt to more precisely define the EEG characteristics of this disorder we reviewed multiple 24-hour polygraphic records of 67 children with infantile spasms (Hrachovy et al., 1984). As a result of this study we were able to define 5 relatively distinct patterns which, although not entirely consistent with the original definition of hypsarrhythmia, did retain two basic features: very high voltage and some degree of interhemispheric asynchrony. In addition, these particular patterns were associated with the same types of clinical seizures and the same types of ictal EEG events as the classical hypsarrhythmic pattern. Consequently, it seemed reasonable to consider these patterns, all of which had previously been recognized by other investigators to occur in association with infantile spasms, as variants of hypsarrhythmia. The term 'variant' is preferred over 'modified' since these patterns do not necessarily evolve from the classical hypsarrhythmia pattern (although this can occur over time in some cases), and are sometimes seen as the initial, or only, EEG configuration. In addition, some of these patterns can appear sporadically, appearing and disappearing over time, and more that one type (including the classical form) can be present within the same record.

Hypsarrhythmia with increased interhemispheric synchronization In this variant the multifocal spike/sharp wave activity and the high amplitude chaotic slow activity characteristic of the classical hypsarrhythmic pattern (Fig. 5.1) is replaced by a better organized pattern in which there is a significant degree of interhemispheric synchrony and symmetry. This may be manifested as bursts of generalized synchronous spike and wave activity, and/or by the appearance of synchronous and rhythmic background activity (Fig. 5.2). This pattern is not necessarily constant, and the record may at times change to one with little or no synchronized activity, and consequently be consistent with classical hypsarrhythmia.

Asymmetrical hypsarrhythmia This pattern is characterized by the presence of hypsarrhythmia with a consistent voltage asymmetry between the hemispheres. The asymmetry may be either regional (i.e., involving only a localized area) or generalized (Fig. 5.3), and, if the degree of asymmetry is both pronounced and generalized, unilateral hypsarrhythmia, or hemihypsarrhythmia results. Because asymmetrical hypsarrhythmia is typically associated with underlying structural abnormalities of the brain (see section 2.5, below), the voltage asymmetry is usually consistently present throughout the record, although the hypsarrhythmic component itself may be variable. The side demonstrating the hypsarrhythmic activity may be the more abnormal hemisphere, or, conversely, the more normal hemisphere.

Hypsarrhythmia with a consistent focus of abnormal discharge In this variant there is a persistent focus of spike/sharp wave, or spike-and-wave activity superimposed on a typical hypsarrhythmic background pattern with multifocal discharges of variable configuration (Fig. 5.4). In some cases there may be focal electrographic seizure activity which can be accompanied by clinical seizures of partial type (see Chapter 8). The epileptogenic foci observed in this variant tend to be persistent, and may remain even after disappearance of the background hypsarrhythmic pattern.

Hypsarrhythmia with episodes of voltage attenuation The hypsarrhythmic pattern in this variant is intermittently interrupted by episodes of markedly decreased voltage that typically persist for 2 to 10 seconds. The attenuation episodes may be localized, regional, or generalized, and in some cases occur in a semiperiodic fashion (Fig. 5.5) resulting in a suppression-burst pattern (Hoefer et al, 1963; Charlton and Mellinger, 1970). This variant is most frequently present during NREM sleep (Watanabe et al., 1993), and in some cases occurs exclusively at this time. Episodes of voltage attenuation can also be observed as an ictal pattern accompanying epileptic spasms (section 3, below).

Hypsarrhythmia without spike or sharp-wave activity This rare variant consists primarily of high voltage, bilaterally asynchronous, slow wave activity (Fig. 5.6), and is associated with little or no spike/sharp-wave components (Gibbs and Gibbs, 1952). As with some of the other variants, this pattern can be present intermittently, and may be state related (e.g., only during wakefulness).

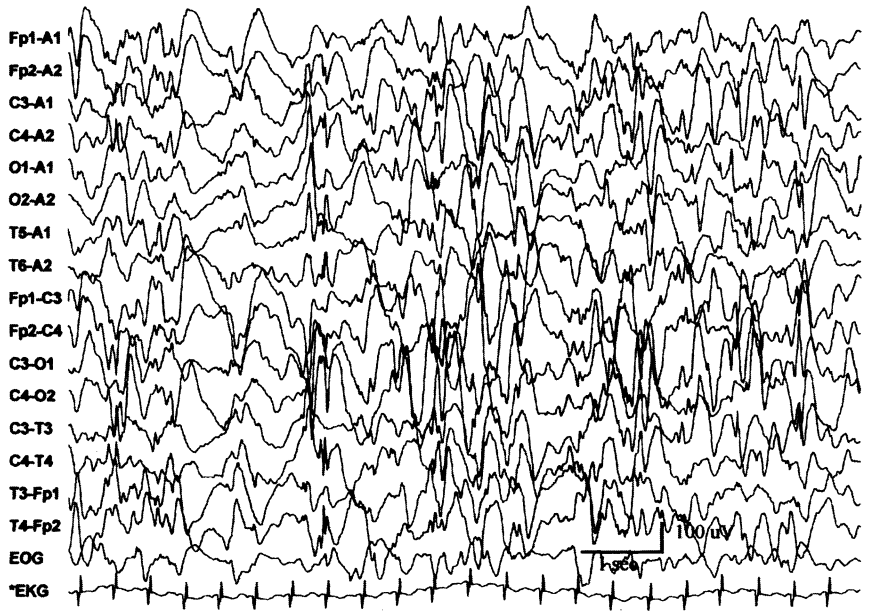

Figure 5.1 Classical hypsarrhythmia Representative sample from an 8 month old male.

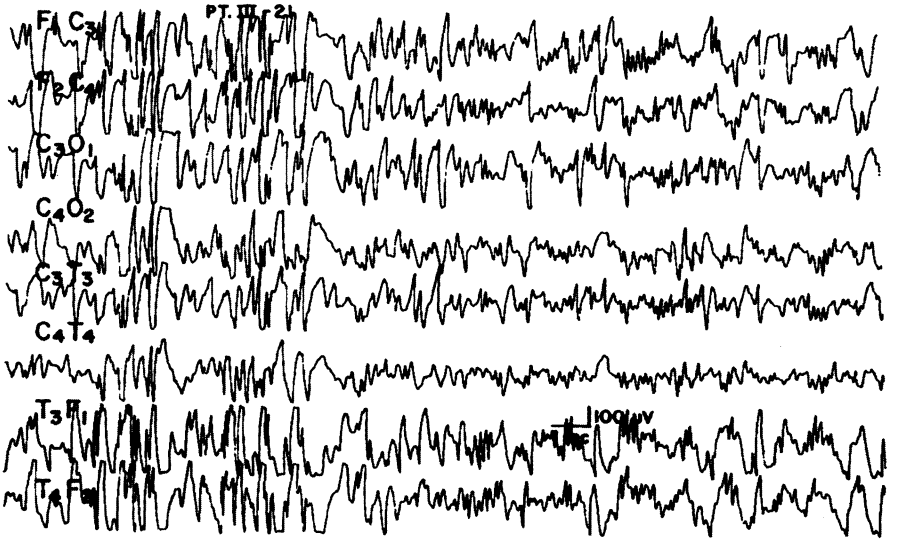

Figure 5.2 Hypsarrhythmic variant with increased interhemispheric synchronization. 9-month old infant. The EEG is characterized by runs of rhythmic, synchronous, and symmetrical alpha frequency activity in all channels. There are also bursts of synchronous, frontal-dominant spike/sharp and slow wave activity. (Reprinted from *Epilepsia*, Vol. 25, Hrachovy, R. A., Frost, J. D., Jr. and Kellaway, P. Hypsarrhythmia: Variations on the theme. Pages 317-325, copyright 1984, with permission from Blackwell Publishing)

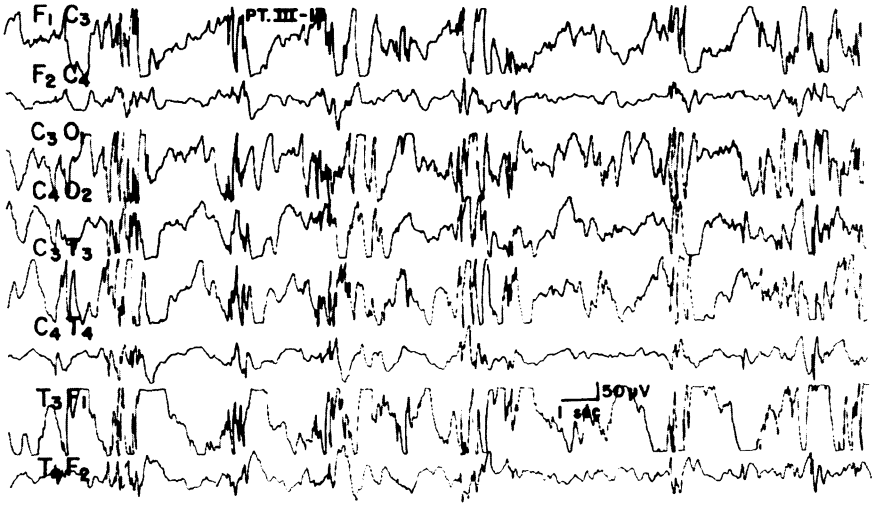

Figure 5.3 Asymmetrical hypsarrhythmia. 6-month old infant with porencephalic defect in right hemisphere demonstrated by CT. . (Reprinted from *Epilepsia*, Vol. 25, Hrachovy, R. A., Frost, J. D., Jr. and Kellaway, P. Hypsarrhythmia: Variations on the theme. Pages 317-325, copyright 1984, with permission from Blackwell Publishing)

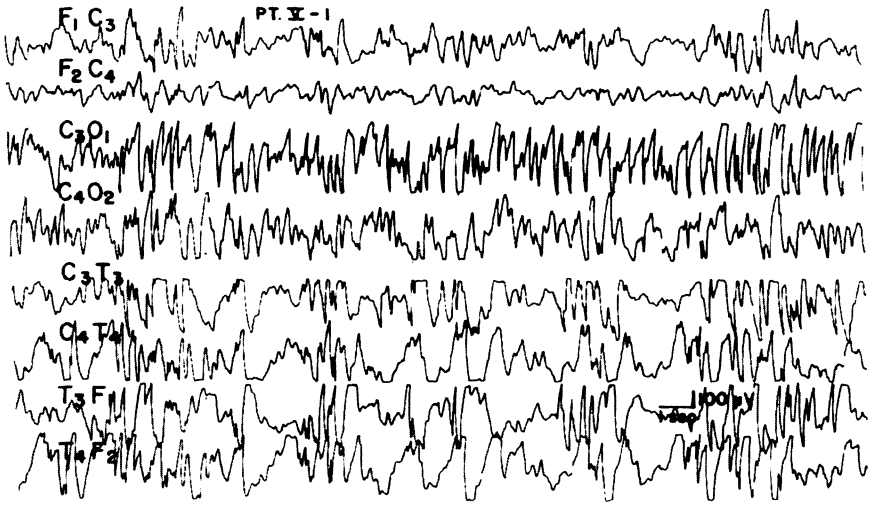

Figure 5.4 Hypsarrhythmic variant with a consistent focus of abnormal discharge. 3-month old infant. The EEG shows a distingushable focus of irregular spike/sharp-and-slow wave activity in the left occipital region. (Reprinted from *Epilepsia*, Vol. 25, Hrachovy, R. A., Frost, J. D., Jr. and Kellaway, P. Hypsarrhythmia: Variations on the theme. Pages 317-325, copyright 1984, with permission from Blackwell Publishing)

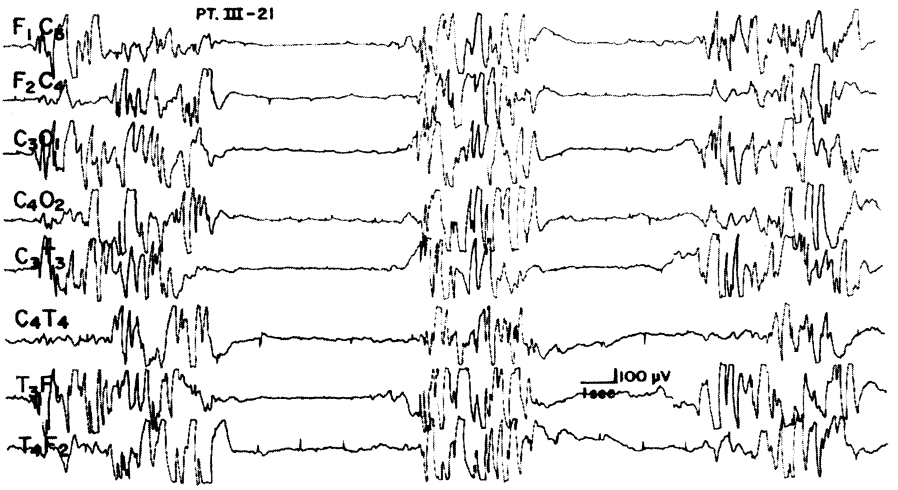

Figure 5.5 Hypsarrhythmic variant with episodes of generalized voltage attenuation. 9-month old infant. The EEG shows semiperiodic episodes of marked voltage attenuation, resembling a suppression-burst pattern. (Reprinted from *Epilepsia*, Vol. 25, Hrachovy, R. A., Frost, J. D., Jr. and Kellaway, P. Hypsarrhythmia: Variations on the theme. Pages 317-325, copyright 1984, with permission from Blackwell Publishing)

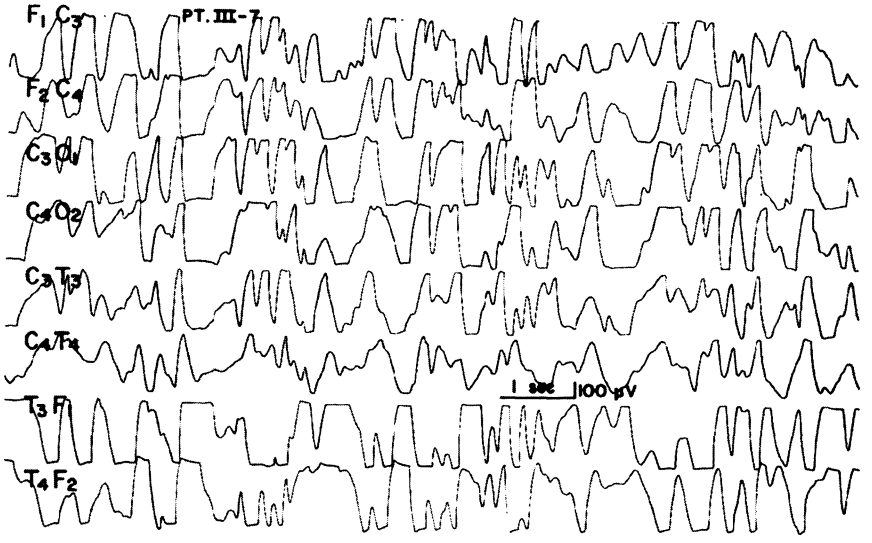

Figure 5.6 Hypsarrhythmic variant characterized by the presence of high-voltage, primarily asynchronous, slow activity with little spike or sharp-wave activity. 13-month old infant. (Reprinted from *Epilepsia*, Vol. 25, Hrachovy, R. A., Frost, J. D., Jr. and Kellaway, P. Hypsarrhythmia: Variations on the theme. Pages 317-325, copyright 1984, with permission from Blackwell Publishing)

Alva-Moncayo et al. (2002) confirmed this classification and provided relative frequencies based upon analysis of 100 cases. The variant with increased interhemispheric synchronization was most common, occurring in 35% of their cases, followed by hypsarrhythmia with a consistent focus of abnormal discharge (26%), asymmetrical hypsarrhythmia (12%), hypsarrhythmia with episodes of voltage attenuation (11%), and hypsarrhythmia without spike or sharp-wave activity (7%).

2.2 Factors influencing the hypsarrhythmic pattern

Based upon information acquired during multiple long-term monitoring studies (i.e., 12-24 hours, or longer), it is now known that hypsarrhythmia is a highly dynamic pattern, with significant changes often occurring during a single recording in relationship to sleep states. It has also been established through the use of serial EEG recordings that this pattern evolves over longer periods of time (i.e., weeks to months), reflecting differing clinical states of the patient associated with natural evolution of the disorder, and or response to therapy.

Sleep state During NREM (slow-wave) sleep there is typically increased amplitude of the hypsarrhythmic background activity, and a tendency for grouping of the spike, sharp, and slow-wave discharges, such that the tracing may assume a periodic appearance (Hrachovy et al., 1981, 1984, Watanabe et al., 1993). As noted above, attenuation episodes also occur frequently during NREM sleep and may result in a suppression-burst pattern. Conversely, during REM sleep the amplitude is often markedly reduced, and there may be a complete disappearance of the hypsarrhythmic pattern for the duration of this stage (Hrachovy et al., 1981) (Fig. 5.7). A transient reduction in the amplitude, or complete disappearance of hypsarrhythmia, is also observed in many patients immediately upon awakening from sleep (Hrachovy et al., 1984), and this normalization has been observed to persist from a few seconds to many minutes before the abnormal pattern resumes (Fig. 5.8).

Ictal events Following a seizure event, the EEG sometimes exhibits a transient period of decreased abnormal activity during which the background pattern may appear relatively normal (Kellaway et al., 1979).

Evolution with time While Gibbs and Gibbs (1952) observed that the hypsarrhythmic pattern tended to decrease with age, they did not provide further information regarding the time course of this evolution. Livingston et al. (1958) performed serial EEG studies on 351 patients with infantile spasms and hypsarrhythmia, and determined that this pattern disappeared in 330 cases (94%) by the age of 5 years, and in 100% of the patients by age 7 years. However, although the pattern may persist to a chronological age of 5-7 years (or rarely longer) the developmental status of those patients is usually equivalent to less than 1-2 years. Kellaway (1959) found that the most common evolution was to a pattern showing a relatively normal background with a discrete spike focus, or

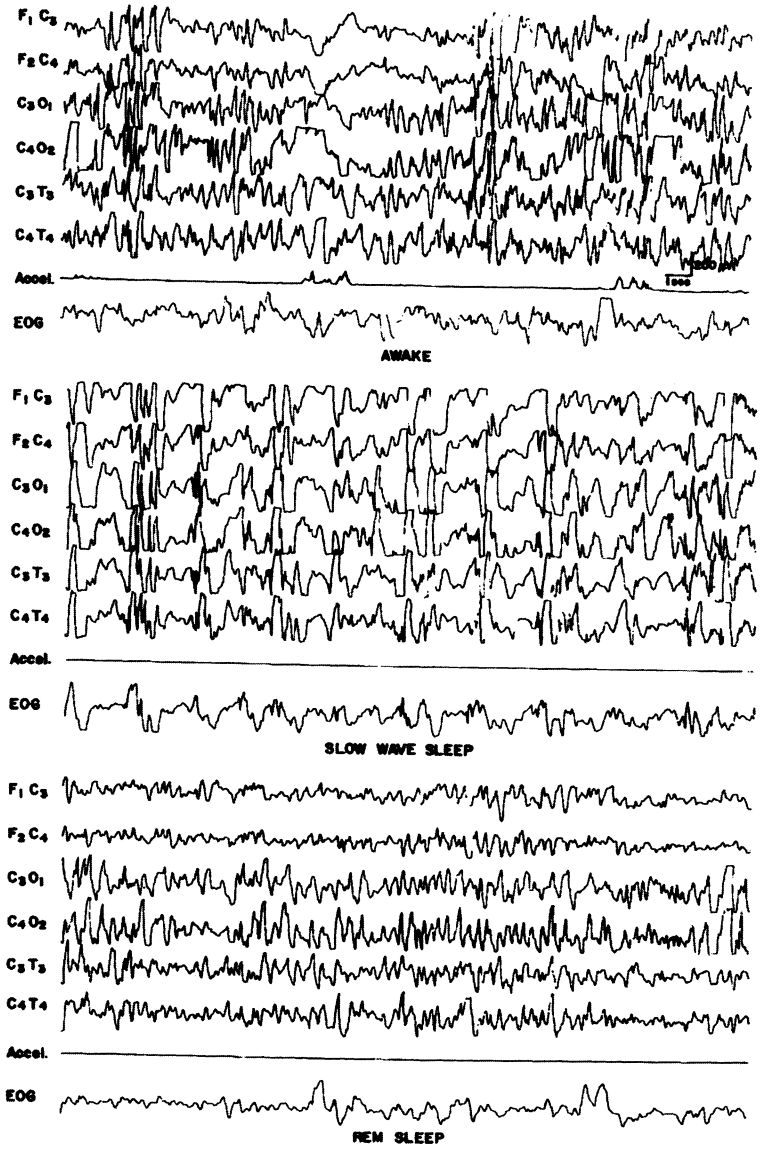

Figure 5.7 Effects of sleep/wakefulness transitions on EEG characteristics. A. During wakefulness a variant hypsarrhythmic pattern is present, with grouping of the spike/sharp and slow-wave activity. B. A more typical hypsarrhythmic pattern is associated with NREM sleep. C. Disappearance of the hypsarrhythmic pattern during REM sleep. (Reprinted from *Neurology*, Vol. 31, Hrachovy, R. A., Frost, J. D., Jr. and Kellaway, P. Sleep characteristics in infantile spasms. Pages 688-693, copyright 1981, with permission from Lippincott Williams & Company)

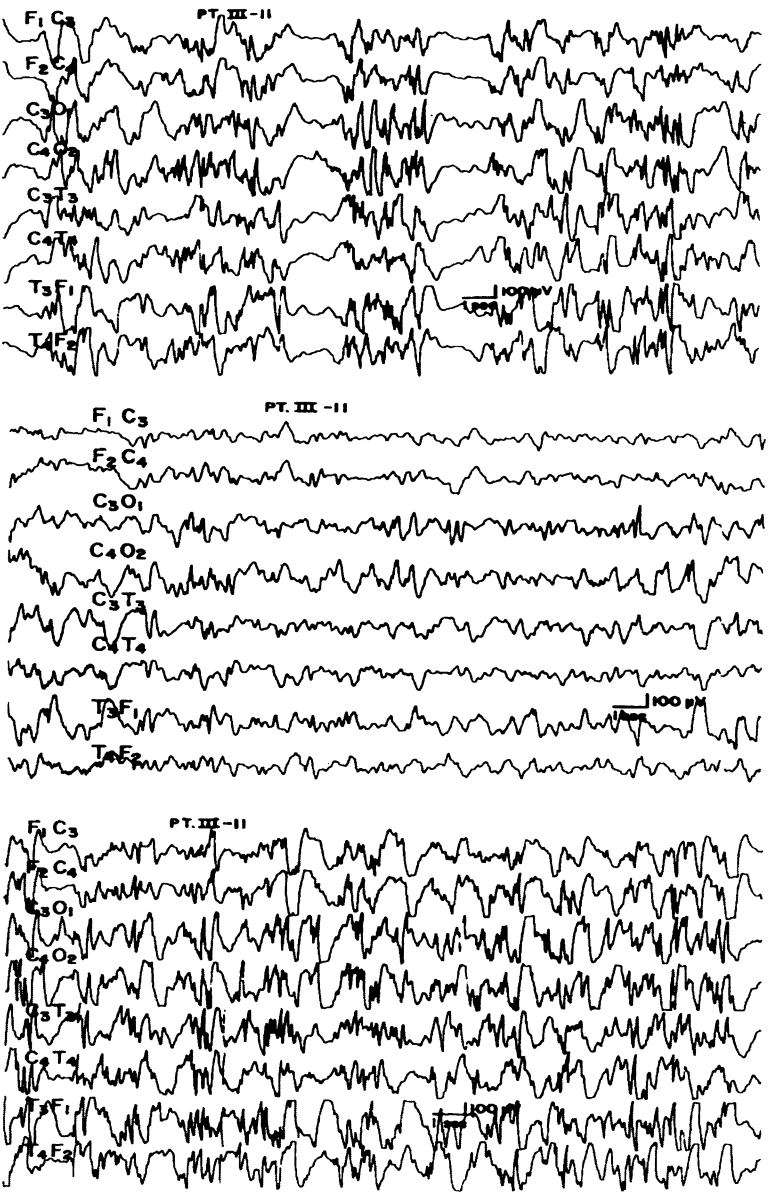

Figure 5.8 Transient disappearance of hypsarrhythmia following arousal. 4-month old infant. A. Hypsarrhythmic pattern present during NREM sleep. B. Immediate post-awakening tracing with absence of hypsarrhythmia. C. Ten minutes after arousal tracing shows return of the hypsarrhythmic activity. (Reprinted from *Epilepsia*, Vol. 25, Hrachovy, R. A., Frost, J. D., Jr. and Kellaway, P. Hypsarrhythmia: Variations on the theme. Pages 317-325, copyright 1984, with permission from Blackwell Publishing)

multiple spike foci. Less common patterns included diffuse high voltage fast activity during sleep, paroxysmal slow activity while awake, a monorhythmic waking pattern of approximately 6 Hz, and, rarely, a completely normal pattern. Negaro et al. (1980) followed 107 children with hypsarrhythmia and infantile spasms to 5-7 years of age, and found that only 3 patients (3%) continued to have hypsarrhythmia. EEGs were normal in 16% of these cases, and 81% had other abnormalities. Kotagal (1995) reported that 63% of 40 patients with hypsarrhythmia exhibited a long-term transition to a pattern characterized by multifocal and generalized spikes prior to evolving ultimately to a slow spike-wave pattern characteristic of the Lennox-Gastaut syndrome (see Chapter 7). Hughes et al. (1997) specifically evaluated the long-term changes of hypsarrhythmia in a group of 505 patients. They observed that while all subjects had both hypsarrhythmia and infantile spasms at some point in time (as a requirement for inclusion in the study), these features were independent at some time in 15% of the patients. They found that the hypsarrhythmic pattern typically persisted for less than 1 month, but documented durations to as long as 7 years. Transition to another pattern (e.g., focal discharges or spike and bilateral spike-wave complexes) typically occurred at around 3 years of age.

Following treatment Harris (1964) found that ACTH treatment of infantile spasms was often associated with an improvement of the EEG, and described a progressive change, with an initial decrease of amplitude, followed by disappearance of the interictal discharges, and finally the appearance of normal rhythms in some cases. She observed that all 6 children in her series of 75 patients who were determined to be essentially normal at follow-up (1-2 years later) had exhibited EEG improvement within 30 days of initiation of ACTH treatment. Vigevano et al. (1993) reported that hypsarrhythmia disappeared within 6-20 days, and the EEG normalized, in 28 of 29 cryptogenic patients treated with ACTH. Gaily et al. (2001) observed a transition from typical hypsarrhythmia to a pattern of multifocal spike activity during treatment with vigabatrin in a number of patients. Table 5.2 summarizes the EEG patterns that were observed in 53 patients at the time of spasm cessation during hormonal therapy with ACTH or prednisone (Hrachovy and Frost, 2001).

Kurokawa et al (1979) reported that intravenous diazepam resulted in suppression of the hypsarrhythmic pattern in 4 of 16 patients, and that these patients had a good response to ACTH therapy. Conversely, only 1 of 11 patients with poor suppression of hypsarrhythmia responded to ACTH. Dulac et al. (1993a) found that acute (IV) administration of diazepam produced a disappearance of spike activity in 15 of 35 cryptogenic patients, and all of these patients had a favorable outcome. Spikes were not suppressed in all 12 infants with an unfavorable outcome. Silva et al. (1996) reported that IV diazepam resulted in disappearance of the hypsarrhythmic pattern, in several patients with Down syndrome and concurrent infantile spasms. Intravenous administration of clonazepam was followed by significant normalization of the EEG in 4 of 14

Table 5.2 **EEG characteristics documented at the time of spasm cessation in 53 patients receiving ACTH or prednisone therapy***

EEG Characteristics	Percent of patients
Hypsarrhythmia	0
Normal	9
Normal background features	32
Sharp/spike and slow-wave foci	30
Temporal region only	15
Temporal and other regions	15
Focal slow activity in temporal region	4
Intermittent rhythmic bifrontal sharp-and-slow-wave activity	3
Unilateral suppression of background activity	6
High voltage fast activity	8
Abnormally slow and disorganized background activity	59
Alpha rhythm present	21
Sharp/spike and slow-wave foci	51
Temporal region only	15
Temporal and other regions	30
Other regions only	3
Intermittent rhythmic bifrontal sharp-and-slow-wave activity	11
Intermittent rhythmic bifrontal delta activity	19
Intermittent rhythmic bi-occipital delta activity	8
Unilateral suppression of background activity	8
No foci	2

* Based on data from: Hrachovy and Frost, 2001.

patients (29%) with infantile spasms, and, while these infants also responded to oral clonazepam, the effect was usually transient (Iinuma et al., 1978).

Precursors of hypsarrhythmia Kellaway (1959) observed that hypsarrhythmia might not be present in the early stage of infantile spasms, especially if the infant was younger than a month or so, and instead, there could be marked asynchrony and shifting foci of irregular, polymorphic discharges. He reported that the typical hypsarrhythmic pattern could then develop over time

and be evident in subsequent studies. Watanabe et al. (1987) found that infants who developed focal, and then multifocal epileptiform discharges in early infancy (age 2-3 months) were likely to develop hypsarrhythmia at around 4-5 months of age. Okumura et al. (1996) followed 21 preterm children with periventricular leukomalacia, and found that all 6 patients who later developed infantile spasms and hypsarrhythmia exhibited an EEG pattern characterized by bilateral, parieto-temporal dominant, polyspike and wave activity in the neonatal period. Iinuma et al. (1994) evaluated 17 infants with visual abnormalities and occipital dominant EEG discharges initially, who eventually developed typical hypsarrhythmia. In addition, as discussed in Chapter 7, suppression-burst patterns as seen in the Ohtahara syndrome may evolve into a more typical hypsarrhythmic pattern. Additional evidence supporting these precursor patterns has been reported more recently (Yanagawa et al., 1993; Okumura and Watanabe, 2001).

2.3 Other interictal EEG patterns

While hypsarrhythmia and its variants are the most common interictal patterns associated with infantile spasms, it has long been recognized that children with characteristic spasms sometimes exhibit other EEG features (Table 5.1). For example, in a study of 73 patients with infantile spasms Druckman and Chao (1955) found that 37% of the cases had abnormal EEGs that were not consistent with hypsarrhythmia (or hypsarrhythmia with increased interhemispheric synchrony), and these included single spike foci, multifocal abnormalities, a slow spike and wave pattern, abnormally slow or fast patterns, paroxysmal slow or fast bursts, continuous spindling, and focal depression. In addition, 6 patients (8%) were reported to have normal EEGs. This has been confirmed by many other investigators since that time, who have noted other patterns as well (Livingston et al., 1958). In view of what is now known regarding the short-term dynamic nature of hypsarrhythmia, as well as its tendency to evolve to other patterns over time, and the fact that many studies reporting other EEG patterns were based on single, time-limited, routine electroencephalograms, it is likely that many such patients actually did have hypsarrhythmia at some time during the course of the disorder. Several studies that have included the use of serial EEG recordings support this view. Jeavons and Bowers (1964) reported that non-hypsarrhythmic EEGs were more common in patients who developed infantile spasms early in life (<5 months of age), and 7 of 11 such cases in their series (in which serial EEG studies were conducted) eventually developed hypsarrhythmia. The study of Hughes et al. (1997) noted above (section 2.2) also demonstrated that other EEG patterns could be seen at times in patients who had previously, or subsequently, had hypsarrhythmia.

Hattori et al. (2001) studied the magnetoencephalographic (MEG) characteristics of 14 patients who either had infantile spasms, or who had previously had the disorder. Essentially all subjects who were still having

spasms at the time of the evaluation had a widespread, bilateral distribution of dipoles (whether or not the MRI was focal), while those patients who had evolved to have other seizure types (partial or generalized) demonstrated regional or focal dipole concentrations.

2.4 Significance of the interictal patterns

Diagnostic value Hypsarrhythmia (including its variants) is a very strong diagnostic indicator for the presence of infantile spasms. While infantile spasms can be present in the absence of hypsarrhythmia, as discussed above, the converse is only rarely the case, and this EEG pattern is seen almost exclusively in this disorder. Occasional cases in which hypsarrhythmia was present in subjects not experiencing clinical spasms have been reported (Baird and Borofsky, 1957; Bower and Jeavons, 1959; Jeavons and Bower, 1964), but these studies did not use 24-hour EEG/video monitoring, and thus it can not be concluded that spasms (particularly those of subtle character) were definitely absent (see Chapter 11, section 1.2, and Chapter 4, section 3).

Correlation with etiology The presence of an asymmetrical or focal interictal EEG pattern has been correlated with a symptomatic etiology in a number of studies. Parmeggiani et al. (1990) quantified the relative amounts of diffuse and focal slow activity present in 24 patients with hypsarrhythmia and infantile spasms. They found that the diffuse component predominated in the 8 subjects with a cryptogenic etiological classification, while the focal component was seen most frequently in patients with brain lesions of prenatal etiology (tuberous sclerosis). Watanabe et al. (1993), in a study of 82 patients with hypsarrhythmia, found that asymmetric hypsarrhythmia occurred only in symptomatic subjects. In a study that included 77 infantile spasm cases, Donat and Lo (1994) identified 22 cases in which the hypsarrhythmic pattern was either unilateral or lateralized. Nineteen (86%) of these patients had focal or lateralizing features during diagnostic imaging (CT or MRI). Conversely, 16 of 17 (94%) patients classified as cryptogenic had symmetric hypsarrhythmia. Similar correlations between asymmetric hypsarrhythmia and underlying structural abnormalities have been observed in several other studies (Miyazaki et al., 1994b; Drury et al., 1995; Gaily et al., 2001). Kramer et al. (1997b) reported that patients with cerebral dysgenesis were more likely to exhibit hemihypsarrhythmia or a suppression-burst variant, while subjects with a history of perinatal hypoxia-ischemia were likely to show an absence of normal sleep patterns.

Correlation with outcome This topic is covered in Chapter 12 (Long-term Outcome), section 3.3 (Predictive factors: EEG characteristics at diagnosis and following therapy).

3. ICTAL EEG PATTERNS

3.1 Description of ictal events

The ictal EEG event typically accompanying a spasm was described by Gibbs and Gibbs (1952) as a discharge of fast activity mixed with high voltage spikes, with a longer duration than the discharge usually associated with a myoclonic seizure. Kellaway (1959) reported two patterns that could be associated with the ictal event: a polyspike and wave burst, or a sudden depression of electrical activity that slightly outlasted the motor component. Both Iwase and Watanabe (1972) and Horita et al. (1977) described bursts of fast (14-19 Hz) EEG activity accompanying some clinically evident ictal events. Following the advent of time-synchronized EEG/polygraphic/video monitoring it became possible to more fully characterize the entire spectrum of ictal EEG patterns which can be seen in this disorder. Kellaway et al. (1979) characterized 5,042 seizures recorded during 24-hour monitoring studies involving 24 infants with infantile spasms, and identified 11 different ictal EEG patterns that occurred in association with the clinical events (Table 5.3): (1) a high-voltage, frontal-dominant, generalized slow-wave transient followed by a period of voltage attenuation that was present in 37.9% of the seizures; (2) a generalized sharp and slow-wave complex, seen in 17.4% (Fig. 5.9); (3) a generalized sharp and slow-wave complex followed by a period of voltage attenuation, found in 13.2%; (4) a period of voltage attenuation only, found in 11.9%; (5) a generalized slow wave transient only, seen in 10.9%; (6) a period of voltage attenuation with superimposed fast activity (Fig. 5.10), present in 6.9%; (7) a generalized slow-wave transient followed by a period of voltage attenuation with superimposed fast activity, seen in 1.3%; (8) a period of attenuation and rhythmic slow activity, in 0.2%; (9) fast activity only, in 0.2%; (10) a sharp and slow-wave complex followed by a period of voltage attenuation with superimposed fast activity, in 0.1%; and (11) a period of voltage attenuation with superimposed fast activity followed by rhythmic slowactivity, in 0.1%. During this study it was found that particular types of ictal EEG events did not correlate closely with specific types of clinical events. However, motor spasms (flexor, extensor, and mixed) were most frequently associated with a high-voltage generalized slow-wave transient followed by a period of attenuation (pattern 1, above), while "arrest" attacks and asymmetrical spasms were typically accompanied by periods of voltage attenuation with superimposed fast activity (pattern 6, above). The durations of the ictal EEG events ranged from 0.5 to 106 seconds, with the longer episodes associated with the arrest phenomenon. It was also observed that episodes of generalized voltage attenuation sometimes occurred (both awake and asleep) without evidence of a clinical seizure.

Many subsequent investigations have provided confirmation for the existence of most of the ictal patterns described by Kellaway et al. (1979) and listed in

Table 5.3 **Ictal EEG patterns in infantile spasms***
(Total number of ictal events = 5042)

Ictal Pattern	*%*
1. Slow wave → attenuation	**37.9**
2. Sharp and slow wave	**17.4**
3. Sharp and slow wave → attenuation	**13.2**
4. Attenuation	**11.9**
5. Slow wave	**10.9**
6. Attenuation/fast activity	**6.9**
7. Slow wave → attenuation/ fast activity	**1.3**
8. Attenuation and rhythmic slow activity	**0.2**
9. Fast activity	**0.2**
10. Sharp and slow wave → attenuation/fast activity	**0.1**
11. Attenuation/fast activity → rhythmic slow activity	**0.1**

→ = followed by / = with superimposed

* Adapted from *Annals of Neurology*, Vol. 6, Kellaway, P., Hrachovy, R. A., Frost, J. D. Jr. and Zion, T Precise characterization and quantification of infantile spasms. Pages 214-218, copyright 1979, Little, Brown and Company. Reprinted with permission from Wiley.

Table 5.3 (Yamatogi and Ohtahara, 1981; King et al., 1985; Donat and Wright, 1991a,b; Fusco and Vigevano, 1993; Viani et al., 1994b; Gaily et al., 1995; Haga et al., 1995a,b; Silva et al., 1996; Acharya et al., 1997; Panzica et al., 1999; Wong and Trevathan, 2001; Vigevano et al., 2001; Gaily et al., 2001). The lack of a correlation between the type of clinical spasm (flexor, extensor, or mixed) and the ictal EEG pattern was also confirmed by King et al. (1985). Fusco and Vigevano (1993) have, however, disputed the inclusion of voltage attenuation

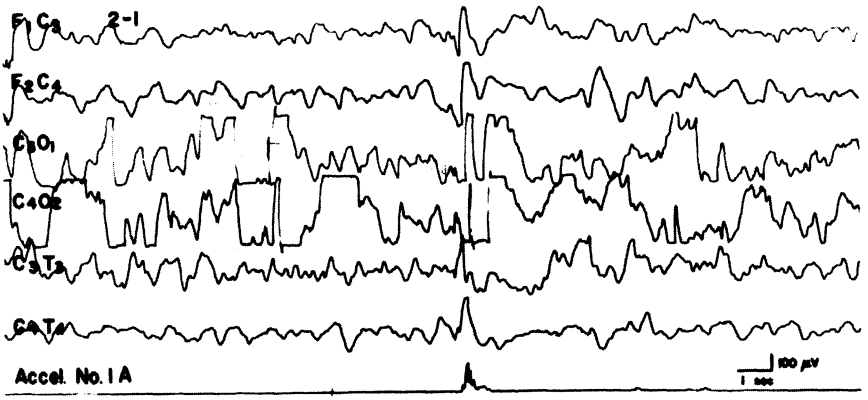

Figure 5.9 Ictal EEG change associated with infantile spasms: high-voltage, frontal-dominant, generalized slow-wave transient.

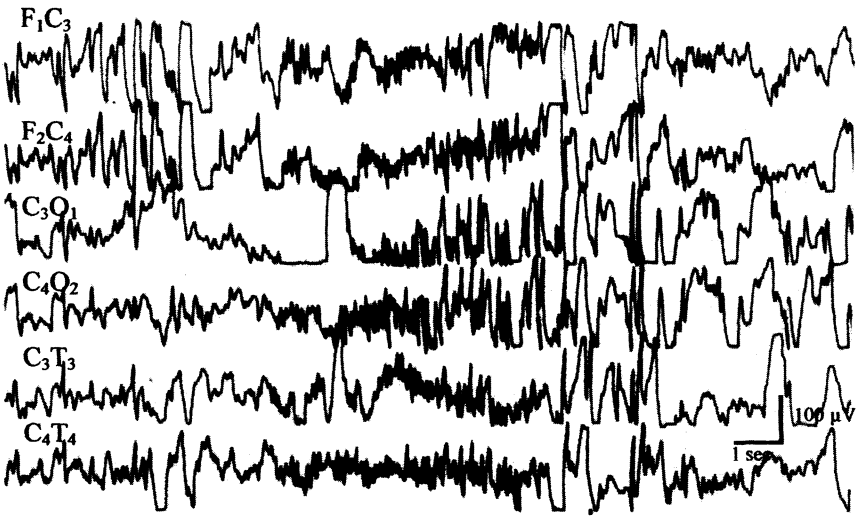

Figure 5.10 Ictal EEG change associated with infantile spasms: a period of voltage attenuation with superimposed fast activity

episodes (decremental activity) as ictal events. These investigators analyzed 955 spasms in 36 cases of infantile spasms, and reported that the attenuation pattern always followed a vertex positive slow wave (in contrast to Kellaway et al. [1979] who found attenuation to be the initial ictal event in 19.1% of the spasms

recorded), and further noted that it always appeared after the clinical spasm. Consequently, they considered the attenuation episodes to be post-ictal, rather than ictal events. These findings are difficult to reconcile with the earlier study, particularly since no slow wave was present at ictal onset in 19.3% of the seizures analyzed by Kellaway et al. (1979). Wong and Trevathan (2001) have also questioned these findings, and noted that some of their patients did not have initial slow waves coincidentally with onset of the clinical spasm, and that the electrodecremental activity was often time-locked with the continuing tonic spasm. King et al. (1985) also had reported that both tonic seizures and arrest episodes could be associated with suppression of background activity which persisted beyond the clinical spasm. Consequently, based on the available evidence, it seems reasonable to continue to include voltage attenuation episodes as probable ictal events.

Panzica et al. (1999) examined the spectral characteristics of ictal EEG events using computer-based analytical techniques in 18 patients with infantile spasms. In 13 of the 18 cases they found that short discharges of fast activity (15-23 Hz) were the initial ictal manifestations, and preceded spasm onset by approximately 500 msecs. This activity tended to be asymmetrical, even in cases exhibiting symmetrical clinical spasms, suggesting the possibility of a localized cortical origin. No slow component was present preceding the spasms in any of these 13 cases, and when it did occur it began after clinical spasm onset. Sharp transient activity preceded spasms in 2 of the 5 cases without ictal fast activity, and the other 3 (all with asymmetrical spasms) had a decrease of spectral power at ictal onset.

A number of investigators have documented the coexistence of partial seizures occurring in patients with infantile spasms, and have observed that in some cases there is an apparent coupling of these two seizure types, with spasms sometimes immediately following partial seizures, and in other instances preceding them. This phenomenon, and its potential significance are considered in Chapter 8.

3.2 Significance of ictal patterns

In a study based on EEG/video monitoring that included 42 patients with infantile spasms, all of whom had hypsarrhythmia, Haga et al. (1995a,b) found that there was no significant correlation between the various types of ictal EEG patterns and etiology (i.e., cryptogenic versus symptomatic), subsequent seizure control, or prognosis for developmental outcome. However, as with the interictal EEG characteristics, the best correlation with etiological factors and outcome has been observed in cases with asymmetrical ictal features, irrespective of the particular pattern. Donat and Lo (1994) evaluated 77 children with infantile spasms, and compared the EEG findings to the results of CT/MRI imaging. Asymmetric ictal patterns were seen in 16 cases (21%), 14 of whom also had asymmetrical or unilateral hypsarrhythmia, and most had focal or

lateralized structural lesions. The most common patterns observed were higher amplitude fast activity and/or more pronounced attenuation episodes on the side of the lesion. It was noted that asymmetrical clinical spasms occurred only in patients with asymmetric ictal EEG patterns. Gaily et al. (1995) evaluated 8,680 spasms in 60 children with infantile spasms, and found that 32% of the ictal EEG events were asymmetric (amplitude on one side more than twice that on the other side) and 6% were asynchronous (> 100 msec difference between sides). Structural brain abnormalities involving the contralateral hemisphere (i.e., the side opposite to the side with the highest amplitude or earliest onset) were significantly more common in children with more than 50% of the events classified as asymmetric or asynchronous. In a more recent study by this group (Gaily et al., 2001) involving 44 infants with infantile spasms it was reported that asymmetrical ictal fast activity occurred significantly more often in symptomatic patients (35% of 31 symptomatic cases) than in cryptogenic cases (8% of 13 cryptogenic cases).

4. SLEEP CHARACTERISTICS

Infantile spasms is typically associated with a significant disturbance of the sleep pattern. In a study that included 32 cases (Hrachovy et al., 1981), we found that the average total sleep time was 22% lower than that of an age matched control group prior to treatment, and that this value did not increase significantly following hormonal therapy, whether or not the treatment was successful. In addition, a number of investigators have observed low values for stage REM sleep in this disorder (Fukuyama et al., 1979; Horita et al., 1979, 1980; Hashimoto et al., 1981; Shimohira et al., 1992; Kohyama et al., 1996). Kohyama et al. (1996) found that the average stage REM time in 17 patients was 33% lower than the corresponding value in age matched control subjects. In our study (Hrachovy et al., 1981) the average stage REM value was 58% below that of the control group. Following hormonal treatment, the stage REM value increased significantly in 8 patients whose seizures were controlled (to a value only 13% below the controls), but did not change significantly in 9 non-responders to therapy. In neither of these two studies did the pre-treatment REM time prove to be of prognostic value, with low values present in both responders and non-responders. However, in a study including 9 patients, Fukuyama et al. (1979) reported that 4 subjects with an unfavorable outcome had less REM time, less slow wave sleep, and increased light sleep, in comparison to the 5 patients with favorable outcomes.

Shimohira et al. (1992) reported that body movement indices (including distributions of gross and twitch movements) were more disturbed in the pretreatment studies of patients who ultimately had a poor outcome, as compared to those with a favorable outcome. Kohyama et al. (1996) found that a measure they termed the phasic inhibition index (PII: the rate of simultaneous occurrence of phasic chin EMG activity and bursts of horizontal eye movements during

REM sleep) was significantly higher before treatment in patients who had a poor prognosis, as compared to those with a favorable outcome. They interpreted this finding to reflect a relative weakness in infantile spasms of the motor inhibition normally occurring during rapid eye movements, and suggested that this might be based on pontine dysfunction. In a subsequent study (Kohyama et al., 2000) it was determined that ACTH therapy was associated with a relative normalization (i.e., decrease) in the PII.

In some patients, ictal EEG events identical to those seen in association with clinical seizures occur during REM sleep, and typically recur in a periodic manner, but are usually not associated with spasms (Iwase and Watanabe, 1972; Horita, 2001). However, Horita et al. (1977) reported a case in which these events were associated with eye movements. Hrachovy et al. (1984) reported that these ictal discharges tended to increase in frequency until the onset of NREM sleep, when they disappeared in association with return of a hypsarrhythmic pattern. However, if the patient awakened from REM sleep, the ictal pattern often continued into the awake state and was then associated with typical clinical spasms (Fig. 5.11).

5. EVOKED POTENTIAL CHARACTERISTICS

Although abnormal brainstem auditory evoked potentials (BAEPs) occurring in association with infantile spasms had been described in several case reports (Watanabe et al., 1976; Yagi et al., 1980; Tanaka and Kaga, 1980), the first systematic study was conducted by Kaga et al. (1982). Abnormalities were found in 9 of 30 cases (30%), and included absence of all components (1 case), absence of waves 2, 3, 4, or 5 (5 cases), and prolongation of the 1-5 interval (3 cases). Three of the 9 cases were clearly in the symptomatic category, but the cause was unknown in 6 patients. These investigators interpreted the results as providing clear evidence for brainstem involvement in infantile spasms. Curatolo et al. (1989) reported similar findings, with BAEP abnormalities documented in 43% of 28 children with infantile spasms, and found no correlation with etiological factors or outcome measures. No brainstem abnormalities were detected by MRI in these patients. Markand et al. (1982) found prolonged interpeak latencies in all patients in a study of four children with nonketotic hyperglycinemia. In three additional studies (Furune et al., 1985; Iyoda et al., 1987; Miyazaki, et al., 1993) BAEP abnormalities were found only in symptomatic patients. In our own series of 18 patients (3 cryptogenic, 15 symptomatic) with infantile spasms and hypsarrhythmia confirmed by EEG/video monitoring, the 1-5 and 3-5 interpeak latencies were normal in all cases, although mild peripheral dysfunction (prolongation of wave 1) was present in 7 patients (unpublished data).

Abnormal visual evoked potentials (VEPs) have been reported to occur in some infantile spasms cases, including both symptomatic and cryptogenic categories, although the number of patients evaluated has been small (Markand

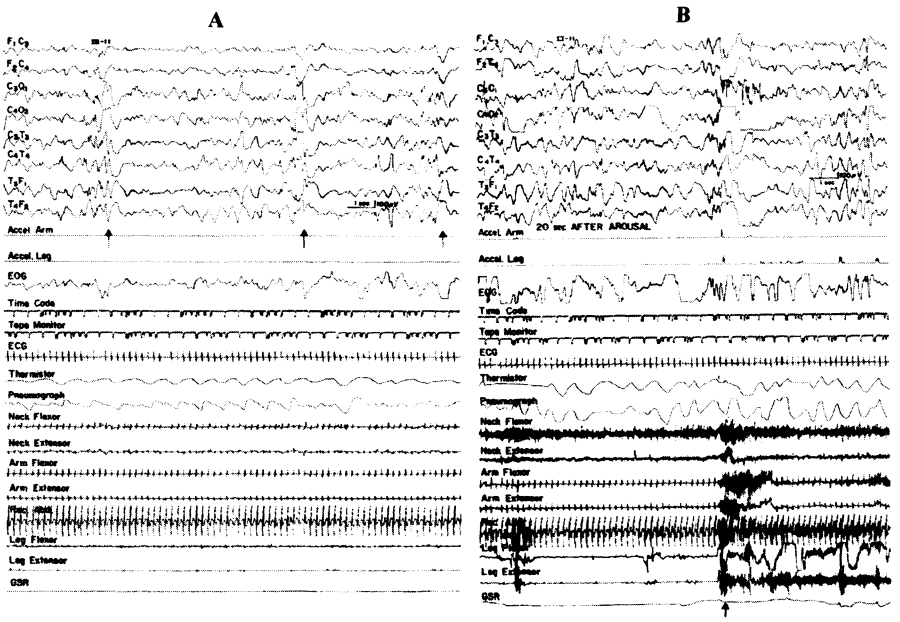

Figure 5.11 Effect of arousal from REM sleep on subclinical ictal EEG events. A. Sample of record near the end of a REM period. Arrows indicate EEG complexes not accompanied by clinically evident spasms (note absence of EMG and accelerometer activity). B. Sample taken 20 secs after awakening. Arrow indicates first clinical spasm, occurring in association with ictal EEG complexes similar to those present during REM sleep. (Reprinted from *Epilepsia*, Vol. 25, Hrachovy, R. A., Frost, J. D., Jr. and Kellaway, P. Hypsarrhythmia: Variations on the theme. Pages 317-325, copyright 1984, with permission from Blackwell Publishing)

et al.,1982; Taddeucci et al., 1984; Yamamoto et al., 1985; Iyoda et al., 1987; Okubo, 1989; Topcu, et al., 2002). Wenzel (1987) found grossly abnormal pattern VEPs in all 8 patients studied, although flash VEPs were normal in 50% of these symptomatic cases. In this same study, early components (<40 msecs) of the somatosensory evoked potentials (SEPs) were normal in all 6 cases evaluated, while late (>100 msec) components were abnormal or missing in all patients. The investigators interpreted these results as consistent with a functional block of these sensory systems resulting from the epileptogenic process. In support of this concept, they observed that following treatment most subjects had significant improvement or normalization of both VEPs and SEPs. In a study that included 10 patients, abnormal SEPs were found in 70% (all symptomatic) by Miyazaki et al. (1992). Abnormalities included absence or decreased amplitude of later components, prolonged N1 latencies, and prolonged P3-N1 interpeak latencies.

6. SUMMARY AND SYNTHESIS

Electroencephalography and time-synchronized EEG/video monitoring are the most important diagnostic procedures available for evaluation of patients with suspected infantile spasms. The interictal EEG is almost always abnormal, and the most characteristic pattern is hypsarrhythmia, characterized by very high amplitude, variably asynchronous, random appearing, slow waves in all areas and high voltage spike/sharp wave activity of variable, usually multifocal, origin. A number of variants of this basic pattern are recognized, based upon features such as increased hemispheric synchrony, presence of voltage asymmetry, consistent foci, and periodicity. Hypsarrhythmia or one of its variants is present in the majority of infantile spasms patients at some time, although other abnormal EEG patterns are seen in a minority of cases, and, rarely, the EEG can be normal. The character of the interictal EEG pattern is influenced by many factors, including sleep/wake status, presence of ictal activity, and response to therapy. Hypsarrhythmia, even in untreated or unresponsive cases, typically evolves over time, and is rarely present after 5-7 years, although the EEG remains abnormal in the majority of cases. The most important prognostic aspect of the interictal EEG pattern is the degree of hemispheric symmetry. Most cryptogenic cases have a symmetrical pattern, while asymmetrical patterns are usually indicative of underlying structural abnormalities. Thus, the presence of an asymmetrical pattern is associated with an unfavorable prognosis for long-term outcome. Other aspects of the interictal EEG have been correlated with etiological or prognostic factors in some studies, but at this time the evidence does not permit definitive conclusions to be drawn.

A variety of EEG configurations have been found to occur in association with spasms or other clinically recognizable ictal events, including various combinations of slow wave transients, sharp waveforms, fast activity, rhythmic slow activity, and episodes of voltage attenuation. The most common pattern is a generalized slow-wave complex, followed by a period of voltage attenuation, which has been found to accompany most motor spasms. In general, however, the type of ictal EEG pattern does not correlate significantly with specific clinical events. Similarly, most studies have not found significant correlations between types of ictal EEG patterns and etiology or prognosis. However, as with interictal activity, asymmetrical ictal EEG patterns do correlate with underlying structural lesions in symptomatic patients, and consequently do suggest an unfavorable outcome.

Abnormal evoked potentials (auditory, visual, and somatosensory) have been documented in some patients with infantile spasms, but no consistent correlations with etiology or outcome have been proven, and there have been few systematic studies involving large patient groups.

The sleep characteristics are usually disturbed in infantile spasms, with most patients exhibiting both decreased total sleep time and a relative decrease of stage REM. Stage REM typically increases in patients who respond to hormonal

treatment. Some studies have also documented disturbances of motor activity during sleep.

7. FUTURE RESEARCH

More definitive information is needed regarding the variability and the evolution of the interictal EEG patterns associated with infantile spasms. This should include studies designed to identify more precisely the EEG characteristics present in the neonatal period that may predict the later occurrence of hypsarrhythmia and other patterns associated with infantile spasms. In addition, more useful criteria, based upon ictal and interictal EEG characteristics, are needed for identifying patients most likely to benefit from medical, as opposed to surgical therapy, and for predicting which patients may have a favorable outcome even if not treated.

Surprisingly, there have been very few evoked potential studies of infantile spasm patients, even though this technique has the potential to provide novel information regarding the functional integrity of central pathways in this disorder. In addition, the few investigations that have been conducted have provided inconsistent results, and this probably reflects the small numbers of subjects in most series. Future studies should be well-controlled to account for normal age-related evolution of evoked potential characteristics, and should include multiple evaluations to detect progressive pathology. Additional research in this area would be expected to provide more specific information regarding the pathophysiology of this disorder, and, specifically, could contribute to knowledge regarding the site of initial dysfunction (e.g., brainstem vs. cortical structures).

Chapter 6

Neurodiagnostic Imaging

1. INTRODUCTION

While in the past most knowledge of the precise anatomy and pathology underlying neurological disorders was obtained by direct examination of tissue obtained at autopsy or during surgical procedures, in recent years greatly improved noninvasive imaging techniques have provided an additional source of information. The improved resolution of X-ray computed tomography (CT) and magnetic resonance imaging (MRI), in comparison to earlier techniques (plain skull x-ray, pneumoencephalography, ventriculography) now permits the identification of structural abnormalities with reliability approaching that of direct examination. In addition, the ability to obtain dynamic information regarding metabolic processes provided by techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) has opened entirely new avenues of research. These methodologies have been applied to the problems associated with infantile spasms, and the results of a number of studies have provided novel information that is relevant to the questions of etiology and pathophysiology.

2. X-RAY COMPUTED TOMOGRAPHY (CT SCANNING)

CT scanning evolved in the late 1960s and early 1970s as a combination of existing X-ray technology and novel analytical and reconstruction algorithms made possible by rapidly developing computer science, to provide the first noninvasive method for imaging brain tissue. Even early systems provided improved diagnostic capabilities in comparison to pneumoencephalography, while eliminating many of the associated risks (Cascino, 1997). This technique

was soon applied in the investigation of infantile spasms, and has subsequently become a standard diagnostic tool.

Many investigators have reported a high incidence of structural brain abnormalities in infantile spasms as revealed by CT scanning. In 15 studies of unselected patients conducted between 1978 and 2001, with population sizes exceeding 25 subjects each (range 26-364 patients), abnormalities were detected in 53-90% of the cases, with an overall average value of 71% (Gastaut et al., 1978; Imamura and Sogawa, 1980; Singer et al., 1982; Lingham and Kendall, 1983; Ludwig, 1987; Coe and Lee, 1989; Takahashi et al., 1990; Howitz et al., 1990; Pedersen et al., 1990; Mahdi et al., 1990; Diebler and Dulac, 1994; Kalinina et al., 1997; Aydinli et al. 1998; Matsuo, 2001a,b; Koul et al., 2001). While a very wide range of specific abnormalities was documented, common findings included cerebral atrophy, ventricular enlargement, encephalomalacia, calcification/hyperdensity, malformations, periventricular leukomalacia, porencephaly, edema, cortical dysplasia, and neoplasms. In several studies it has been observed that abnormal CT findings are seen more frequently in infantile spasms than in most other types of epilepsy (Lingham and Kendall, 1983; Galli et al., 1985; Coe and Lee, 1989).

3. MAGNETIC RESONANCE IMAGING (MRI)

While a great deal of information concerning the structural abnormalities of the brain associated with infantile spasms has been derived over the past 35 years from studies based on CT, the more recent advent of MRI has provided a new level of improved precision. Based on the principle of nuclear magnetic resonance, and using only radio frequency energy and applied magnetic fields, this imaging technique provides very high resolution anatomical information, without the use of ionizing radiation, and poses no known biological hazards. MRI is currently the most sensitive and specific imaging methodology available for the study of brain structure, and has now largely replaced CT as the first choice for the evaluation of patients with epilepsy (Cascino, 1997). This technique has been applied to the study of infantile spasms with increasing frequency over the past 15 years, and the findings have provided new insights into the range of underlying structural abnormalities that can be associated with this disorder. The information obtained during these studies is also relevant to further understanding of the pathophysiological basis of infantile spasms.

3.1 Diagnostic applications

In three recent studies of unselected infantile spasms populations, with group sizes of 64-78 patients each, the number of cases with MRI abnormalities ranged from 58-82%, with an average value of 70% (Aydinli, 1998; Okumura et al., 1998; Wong, 2001). Common findings included cerebral malformations, cerebral atrophy, delayed myelination, ventricular enlargement, basal ganglia/

thalamic abnormalities, encephalomalacia, cerebellar hypoplasia/ atrophy, porencephaly, and tuberous sclerosis. In studies which have evaluated both MRI and CT in the same population, it has been found that most patients who have an abnormal study by one method will also be abnormal by the other (van Bogaert et al., 1993; Aydinli, 1998). However, in occasional cases (Diebler and Dulac, 1994; Aydinli, 1998) the MRI will be abnormal (e.g., delayed myelination, encephalomalacia, cortical dysplasia) in the presence of a normal CT, or vice versa (e.g., cerebral edema, early calcification). While the basic diagnostic yield of 70% for MRI is essentially the same as that reported for CT (71%) in the studies reviewed above (section 2), many investigators have pointed out the improved specificity provided by MRI, which often permits a precise determination of the underlying pathology in symptomatic cases (e.g., dysplasias, malformations), as opposed to non-specific abnormalities (van Bogaert et al., 1993; Diebler and Dulac, 1994; Aydinli, 1998; Galicchio et al., 1999).

3.2 Abnormalities of brain maturation

Because of the age-related occurrence of infantile spasms, it has seemed obvious to most investigators that the pathophysiology of this disorder must in some way be crucially dependent upon the precise maturational sequence of brain development. This possibility has, however, been difficult to evaluate in the past due to the difficulty in measuring maturational features noninvasively and longitudinally. With the recent advent of MRI techniques of greatly improved resolution, as well as the ability to readily acquire and manipulate the images in a 3-dimensional format, it has become possible to begin to study the maturational process in detail, and to correlate identified abnormalities with data obtained from other techniques.

The presence of delayed myelination in some infantile spasms patients, as determined by MRI assessment, has been documented in several studies (Staudt et al., 1994; Schropp et al., 1994; Kasai et al., 1995; Muroi et al., 1996; Natsume et al., 1996; Zhongshu et al., 2001). The proportion of patients exhibiting evidence for delayed myelination is relatively high, ranging from 67-77% in three studies that provided this information (Kasai et al., 1995; Muroi et al., 1996; Natsume et al., 1996). This abnormality was found in 88-100% of the symptomatic patients and in 50-56% of cryptogenic subjects (Kasai et al., 1995; Natsume et al., 1996). While evidence for delayed myelination can be present at the onset of infantile spasms, particularly in patients with evidence for pre- or peri-natal insults (Schropp et al., 1994), it often appears later, with a peak incidence at around 8-10 months (Kasai et al., 1995; Natsume et al., 1996), and may disappear later. Sankar et al. (1995) described 3 cases with initially normal MRI findings who were classified as cryptogenic, but who subsequently had an unfavorable course with refractory seizures. Repeat MRIs at 1-3 years of age were, however, abnormal, and showed lateralized abnormalities of myelination

which corresponded to focal EEG and clinical findings. Two of these patients were treated surgically with subsequent seizure control, and pathological examination of the affected tissue indicated the presence of cortical dysplasia.

In a study involving 216 cases of infantile spasms, Koo and Hwang (1996) reported that 93 patients (43%) had focal cortical lesions confined to one area only. They observed that lesions occurring in the occipital region (in 31% of the subjects) were associated with a significantly earlier onset of spasms (average age: 3.4 months) than were lesions in either the centro-temporo-parietal region (in 62% of the patients, with an average age of 6.3 months) or the frontal area (in 6.5% of patients, with an average age of 9.8 months). They noted that the onset age distribution observed in these patients was very similar to the normal maturational sequence, in which posterior regions are myelinated before temporal and frontal areas. A lowered frequency of cortical lesions in frontal regions, as compared to occipital, parietal and temporal areas, has also been reported in two smaller studies (Hamano et al., 2000; Lortie et al., 2002).

While most MRI-based investigations have been directed primarily to examination of cortical features, two morphometric studies have emphasized brainstem abnormalities as well. Miyazaki et al. (1992) found MRI abnormalities in 9 of 10 patients with infantile spasms, and found evidence for brainstem atrophy in 6 subjects (60%). Ozawa et al. (1998) compared a group of 21 infantile spasms patients with periventricular leukomalacia to a comparable group of patients with periventricular leukomalacia without infantile spasms, and demonstrated smaller sizes of the midbrain, pons and medulla in the infantile spasms group. In addition, cerebellar and brainstem atrophy are typically associated with the PEHO syndrome (Somer, 1993; Tanaka et al., 1997).

4. EMISSION COMPUTED TOMOGRAPHY

Modern positron emission tomography (PET) and single photon emission computed tomography (SPECT) techniques represent an evolution of the older conventional nuclear medicine imaging methodology, combined with advances in computer technology and reconstructive algorithms, which permit two and three dimensional displays of the brain distribution patterns of various radioactive nuclides and radiopharmaceuticals (Fahey, 2001; Maurer et al., 2001; Van Heertum et al., 2001). These techniques can provide functional information of various types since biologically active compounds can be used as the tracers. Quantitative information regarding the distribution patterns can also be obtained through appropriate analysis of the resultant images.

4.1 Techniques

4.1.1 Single photon emission computed tomography

The radioactive compounds administered during SPECT studies emit single gamma rays (photons), which are detected by sensors (gamma cameras) placed and/or rotated around the patient in order to acquire activity from various angles. The accumulated data is then processed by computer techniques which generate reconstructions permitting coronal, sagittal, and transaxial views to be displayed (Maurer et al, 2001). Radionuclides commonly used in SPECT scanning include technetium-99m and thallium-201, and in most applications to infantile spasms this technique has been used to provide a dynamic measure of regional cerebral blood flow, permitting identification of focal and/or diffuse areas of hypo- or hyperperfusion.

4.1.2 Positron emission tomography

The radionuclides used in PET scanning (e.g., fluorine-18, nitrogen-13, carbon-11, and oxygen-15) all emit a positron from the nucleus during decay, which almost immediately is annihilated by combination with an electron to produce two oppositely directed photons. Detectors encircling the head signal an event only if photons are recorded simultaneously by a pair of detectors on opposite sides of the head, indicating a decay event along the pathway between the detectors. This detection scheme is more efficient, and as a result PET provides improved resolution and better sensitivity in comparison to SPECT (Maurer et al., 2001; Van Heertum et al., 2001). The availability of positron-emitting isotopes of carbon, fluorine, nitrogen, and oxygen have also made it possible to develop a wide range of radiopharmaceutical agents that can cross the blood-brain barrier and become incorporated into metabolic pathways, thereby permitting visualization and quantification of both normal and pathological function. The most widely used tracer applied to the study of infantile spasms in recent years is [^{18}F]-flurodeoxyglucose (FDG) which allows the non-invasive study of regional glucose metabolism in both cortical and subcortical regions. Other available tracers can be used to measure additional aspects of brain physiology such as oxygen consumption, regional blood flow, and aspects of neurotransmitter/receptor function.

4.2 Metabolic and perfusional abnormalities

Dulac et al. (1987) were the first to demonstrate abnormal findings in infantile spasms patients through the use of functional imaging. In a ^{133}Xe SPECT study involving 17 cryptogenic patients (all had normal CT scans), they found focal areas of hypoperfusion in 14 subjects (82%). This patient group included 5 subjects in the acute stage of the disorder, and 12 older individuals,

suggesting long-term persistence of the abnormality. The focal regions of decreased cerebral blood flow were predominantly located in the parieto-temporo-occipital regions, and were reported to correlate with the location of focal EEG abnormalities.

Chugani et al (1990) studied a group of 13 children with a history of infantile spasms by means of positron emission tomography (PET). While spasms had ceased in some cases, all children had refractory seizures of some type at the time of the study. Although all 13 patients were considered to be cryptogenic, and had normal findings by routine CT and/or MRI imaging, in 5 of these cases (38%) unilateral hypometabolic regions involving the parieto-occipito-temporal areas were identified by the PET study (which measured the local cerebral metabolic rate for glucose). Four children subsequently had surgical resection of the identified cortical site, and were reported to be seizure-free at follow-up. Neuropathological examination of the resected tissue was consistent with focal cortical dysplasia (see Chapter 10, Section 2.2). In a subsequent expanded study involving 44 patients (Chugani et al., 1992), these findings were confirmed, with 28 subjects (64%) showing focal or regional cortical metabolic abnormalities (22 hypometabolic, 6 hypermetabolic). Of particular interest was the observation that only 11 of the 28 patients (39%) with PET abnormalities also had CT or MRI abnormalities. In addition, in this study it was reported that 32 of the 44 infants (73%) had significantly increased glucose uptake in the lenticular nuclei, which was observed in both cryptogenic and symptomatic subjects, and which was not related to age or treatment status. Thus, these studies, together with the earlier SPECT study of Dulac et al (1987), provided evidence suggesting that many infantile spasms cases considered to be cryptogenic actually have identifiable focal abnormalities, which may involve cortical and subcortical sites, and that in at least some cases focal cortical dysplasia may underlie the cortical dysfunction.

These basic findings have been confirmed in a number of subsequent studies, which have documented the presence of metabolic/perfusional abnormalities within cortical and subcortical sites in many infantile spasms patients by using PET or SPECT techniques (Chiron et al., 1993, 1996; Maeda et al., 1993, 1994, 1995; Miyazaki et al., 1994a; Higuchi et al., 1997; Natsume et al., 1996; Hwang et al., 1996; Haginoya et al., 1998, 2000, 2001; Karagol et al., 2001; Metsahonkala et al., 2002). Many investigators have also observed multifocal, as well as diffuse, patterns of metabolic dysfunction, in addition to the unifocal or regional pattern originally described (Maeda et al., 1993, 1994, 1995; Hwang et al., 1996; Natsuma et al., 1996; Haginoya et al., 2000; Karagol et al., 2001), while in some small series only diffuse changes were observed (Khanna et al., 1994; Sztriha et al., 1997). While Chugani et al. (1990) were able to correlate the focal area of metabolic dysfunction with a specific histopathologically confirmed lesion (cortical dysplasia), a finding noted in other studies as well (see Chapter 10, section 2.2), it is not clear at this time if this is true in all cases. Maeda et al (1993, 1994, 1995) have performed serial PET studies in a number

of infantile spasms cases not treated surgically, and found that in a significant number of cases metabolic abnormalities (focal or diffuse) documented on the initial examination were not present when the patient was reexamined several months later. Conversely, some patients with normal PET studies at the onset, were found to have areas of metabolic dysfunction during a subsequent follow-up study. While in some cases the disappearance of PET abnormalities correlated with seizure control, this was not always the case, and in some patients seizures were present without PET abnormality. This variable, or transitory, character of some focal hypometabolic regions over time has subsequently been confirmed by other investigators (Chiron et al., 1993; Natsume et al., 1996; Metsahonkala et al., 2002). These findings suggest that, at least in some cases, the metabolic dysfunction may be a result of functional abnormalities rather than anatomical lesions. However, Chugani (1994) has pointed out that PET may be normal early in the course of the disorder due to low glucose metabolism of the immature cortex even when the EEG shows focal features, but if repeated later (6-12 months) metabolic abnormalities corresponding to EEG foci may be evident. In support of this possibility, it has occasionally been observed that patients with abnormal MRI findings, but normal PET studies, at the initial examination may, when re-examined several months later, have PET abnormalities (Maeda et al., 1995; Metsahonkala et al., 2002).

The specific hypermetabolism observed within the lenticular nuclei of the majority of infantile spasms patients by Chugani et al. (1992) has not been reported by other investigators (e.g., Maeda et al., 1994; Sztriha et al., 1997), although sporadic metabolic dysfunction is commonly reported in various subcortical sites (Khanna et al., 1994; Haginoya et al., 2000; Karagol et al., 2001).

Few studies using metabolic imaging techniques have compared the ictal and interictal characteristics in infantile spasms patients. Haginoya et al. (2001), using SPECT, found evidence for focal cortical hyperperfusion during the occurrence of spasms in only 8 of 21 patients, with the remainder showing either diffuse alteration or no change. The observed ictal changes did not correlate with the interictal findings, which showed various patterns of abnormal perfusion in 13 subjects. In another study involving 3 patients, using near-infrared spectrophotometry, Haginoya et al. (2002) found a marked increase of cerebral blood volume in the frontal region of one subject shortly before spasm onset, as well as a phasic increase of cerebral blood volume accompanying each spasm of the cluster. However the other two patients showed no significant alterations of this measure during spasms.

5. SUMMARY AND SYNTHESIS

Neuroimaging techniques have undergone a radical transformation over the past 50 years, evolving from simple film-based transmission x-ray methods and

invasive pneumoencephalographic techniques, to the current non-invasive, computer-based, tomographic systems which permit multiple display modes, and which use a variety of detection modalities. Present CT and MRI systems provide very high resolution images of brain structure, and display anatomical information that is comparable in many ways to that obtained by direct observation of brain tissue at autopsy. These modalities are routinely used in the evaluation of infantile spasms patients, and structural abnormalities are detected in approximately 70% of cases. MRI, in particular, often permits a definitive identification of underlying, presumably etiological, factors including various brain malformations, dysplasias, and other specific lesions. These imaging techniques are also crucial for classifying patients as cryptogenic or symptomatic, which in turn is the most important prognostic indicator. In recent years the application of MRI has also resulted in new information regarding abnormalities of brain maturation, and the findings have relevance to the further understanding of pathophysiological mechanisms involved in the genesis of this disorder. A significant proportion of infantile spasms patients have evidence for delayed myelination, which is often transitory. Also, the age of onset of infantile spasms appears, in some symptomatic cases, to be dependent upon an interrelationship between the normal maturational process, and the specific location of cortical lesions. Finally, a number of recent investigations have emphasized the frequent occurrence of brainstem abnormalities, in addition to cortical abnormalities, in this disorder.

The development of SPECT and PET techniques has provided the ability to obtain information regarding brain function through the use of radioactive tracer compounds. SPECT studies typically provide a means to measure alterations of regional cerebral blood flow, while PET applications map regions of altered metabolic function. It has been demonstrated that a high percentage of infantile spasms patients, including those classified as cryptogenic by conventional means, have focal regions of altered perfusion and metabolic function, and several studies have correlated these regions with underlying areas of cortical dysplasia. Subcortical and brainstem functional abnormalities have also been found in some patients. The significance of these metabolic and perfusional abnormalities is still not entirely clear, and in some cases they appear to be transitory, while in others they apparently persist indefinitely.

6. FUTURE RESEARCH

More information is needed regarding the significance of the abnormalities of brain myelination that have been documented in many infantile spasms patients, including approximately one half of those classified as cryptogenic by conventional criteria. While delayed myelination can be seen at the onset of the disorder in some cases, such as symptomatic patients with a history of pre- or perinatal insult, in many other cases it does not appear until months later. Consequently, it is not clear if this phenomenon is a part of the specific

pathophysiological process responsible for the genesis of infantile spasms, or if it merely represents a secondary process, developing in some patients only after unknown primary factors trigger onset of the disorder. Answers to these questions would be expected to significantly further our understanding of the role that altered maturational processes play in the causation of infantile spasms, and possibly help explain why so many, seemingly independent, etiological factors can lead to the same clinical syndrome.

Additional studies are also needed in order to clarify the significance of focal regions of altered cortical metabolism and/or cerebral blood flow that have been documented in many patients by functional imaging techniques. One critical question concerns the relationship of such localized regions to underlying cortical anatomy and physiology. If these foci are a result of structural anomalies such as regional cortical dysplasia, presumably present since embryonic development, why are they sometimes transient, either disappearing over time, or appearing for the first time only late in the disorder? If some such metabolic/perfusional abnormalities reflect purely functional alterations in underlying physiology, as some investigators have speculated, how can the two alternative mechanisms be differentiated in individual cases? A related question pertains to the presumed epileptogenicity of these focal abnormalities. Why does their disappearance (or persistence) over time not always correlate with seizure control (or lack of control)? Answers to these questions are crucial in view of increasing interest in the use of surgical resection of cortical lesions as a therapeutic option in medically refractory patients.

Another unresolved area concerns the use of PET and SPECT findings as a basis for the classification of individual patients into cryptogenic or symptomatic categories. The cryptogenic/symptomatic classification scheme, based on clinical history, neurological evaluation, and CT/MRI findings, has proven to have considerable practical value as a prognostic indicator for both long-term mental development and likelihood of seizure control (see Chapters 11 and 12). If PET/SPECT findings are incorporated into this classification process, the number of cryptogenic cases decreases markedly, from around 20% to 5% or less. Further long-term studies are needed in order to determine if this process results in an improved ability to identify those individuals with a favorable prognosis, or if it may possibly result in the unwarranted classification of some patients as symptomatic on the basis or transient functional abnormalities.

Finally, it should be emphasized that there are numerous potential applications of the newer neurodiagnostic imaging techniques that could provide more definitive information regarding the pathophysiology of this disorder. PET, for example, offers the opportunity to explore altered metabolic pathways more carefully through the use of specific radiopharmaceuticals, and SPECT is well suited to examine altered distributions of central neurotransmitter receptors through the use of radioactive receptor binding ligands. Advances in MRI technology offer additional possibilities, including studies of regional blood flow without the use of ionizing radiation through the use of functional magnetic

resonance imaging (fMRI), and even more precise structural imaging of brain tissue through the use of diffusion weighted imaging.

Chapter 7

Differential Diagnosis and Related Syndromes

1. INTRODUCTION

The ictal events (i.e., epileptic spasms) that are typically associated with West syndrome have characteristic features that, if recognized, usually permit this disorder to be identified with a reasonable degree of certainty by the physician (see Chapter 4). However, the short duration of the events, their often sporadic occurrence, and their sometimes subtle motor expression not uncommonly make it very difficult, or even impossible, for observers to accurately determine such features. Consequently, parents, and other observers, including physicians, not infrequently confuse these ictal behaviors with other phenomena including certain normal movements, particular abnormal behaviors associated with other medical disorders, and other types of epilepsy. In one large study, a correct diagnosis of infantile spasms was made at the time of the original medical evaluation in only 11% of the cases (Bellman, 1983). In fact, the correct diagnosis of infantile spasms is sometimes not made for some time, perhaps months, after onset of the disorder. In contrast, the occurrence of normal events, or certain more benign medical conditions, may falsely be identified as infantile spasms, possibly leading to unwarranted medical procedures and/or treatment. In this chapter, the differential diagnosis of infantile spasms is considered, and the clinical features which best differentiate this disorder are discussed. Knowledge of the features which best delineate these other conditions will often permit the early clinical diagnosis of infantile spasms, although in many cases it will be necessary to use EEG/video monitoring techniques in order to obtain definitive information.

2. NON-EPILEPTIC PHENOMENA

While numerous infant movements, of both normal and abnormal character, can potentially be confused with infantile spasms, relatively few specific entities have been documented. The conditions discussed in this section (Table 7.1) have sometimes been misinterpreted as infantile spasms, or alternatively, true epileptic spasms have occasionally been incorrectly diagnosed as these events.

2.1 Confusion with normal infant behavior

Epileptic spasms can easily be confused with normal infant behavior, especially when they occur infrequently and sporadically, rather than in clusters. The **Moro reflex**, which occurs in normal infants up to the age of 5-6 months, is characterized by rapid abduction and extension, followed by flexion and adduction, of the arms, and thus can closely resemble extensor, or mixed extensor/flexor spasms. The possibility that Moro reflexes, as well as other startle and arousal responses (to auditory, visual, or somatic stimuli) that are associated with rapid motor activity, might be confused with epileptic spasms has been recognized by many investigators (e.g., Kellaway, 1952; Taylor, 1952;

Table 7.1 **Some non-epileptic conditions that may be confused with infantile spasms**

Normal phenomena

Moro reflex

Startle and arousal responses

Sleep starts (hypnagogic jerks)

Rhythmic movement disorder (headbanging)

Other medical conditions

Spasmus nutans

Benign myoclonus of early infancy

Benign neonatal sleep myoclonus

Colic

Transient posturing

Bower and Jeavons, 1959; Jeavons and Bower, 1964; Roger et al., 1964; Lacy and Penry, 1976; Donat and Wright, 1992; Pranzatelli, 2002). The key differentiating feature is the presence of an identifiable precipitating stimulus in the case of Moro reflexes and startle responses, whereas true epileptic spasms almost always occur spontaneously and can be triggered by stimulation only rarely (see Chapter 4, section 3.5). In addition, unlike epileptic spasms, these normal reflex events are not associated with EEG abnormalities.

Most individuals, including infants and children, experience occasional myoclonic jerks involving the legs, and sometimes the arms and head as well, during the transition from wakefulness to sleep. This phenomenon, termed **sleep starts** (hypnagogic jerks, hypnic jerks) may be induced by stimuli, or may occur spontaneously, can be symmetric or asymmetric, and can occur singly or in series (American Sleep Disorders Association, 1997). These events have been identified as imitators of infantile spasms in several cases described by Donat and Wright (1992). Differentiating characteristics include the exclusive occurrence during sleep, while in infantile spasms the ictal events are rare during sleep, and the very brief duration of the myoclonic jerks, as compared to the more prolonged character of epileptic spasms (see Chapter 4, section 3.2). While sleep starts are characterized electroencephalographically by a vertex-negative sharp wave, this normal EEG event differs from the ictal patterns that have been described in association with infantile spasms (see Chapter 5, section 3).

Many children (approximately 67% at 9 months of age) exhibit periods of stereotyped, rhythmic movements beginning immediately prior to sleep onset, and persisting into light sleep. This condition has been given many names in the past (e.g., jactatio capitis nocturna, headbanging, head rolling, body rocking, rhythmie du sommeil, etc.), although currently the preferred term is **rhythmic movement disorder** (American Sleep Disorders Association, 1997). This condition can take many forms, but in terms of potential confusion with infantile spasms, episodes involving repetitive movements of the head in a forward to backward manner, or repeated bending of the torso while in the sitting or semi-reclining supine position, would seem to present the most difficulty. While this condition has long been recognized as an entity that could be confused with infantile spasms (Roger et al., 1964), in practice it can be readily differentiated by the close temporal relationship to sleep onset, and the rhythmical back and forth character of the movements (typically repeating at rates from 2 per second to 1 per 2 seconds) rather than the episodic pattern of epileptic spasms. As with the other behaviors seen in normal children, the EEG shows no abnormal ictal features during the rhythmic movements.

While other types of normal infant behavior, such as posturing, attempts to sit up, tremors, shuddering, twitches, and irritability have been mentioned by some investigators as having the potential to be confused with infantile spasms (Taylor, 1952; Bower, 1969; Donat and Wright, 1992; Fejerman, 1994) there is no evidence that such conditions currently present a significant problem in differential diagnosis.

2.2 Movement disorders

Spasmus nutans, a movement disorder of unknown etiology with onset in early childhood, is characterized by nystagmus, episodic head nodding, and torticollis producing head tilt. It is usually seen in neurologically normal children and typically follows a benign course, although rare cases associated with brain tumors have been reported (Behrman et al., 2000). This condition has been considered in the differential diagnosis of infantile spasms for many years (Roger et al., 1964), although its features are sufficiently distinctive that in most cases the two conditions can be readily distinguished. The peak onset age of spasmus nutans overlaps that of infantile spasms, typically becoming apparent between 5 and 18 months, and rarely persisting beyond 3 years (Kellaway and Glaze, 1982; Aung et al., 1996). However, the head movements associated with this condition can assume a number of forms in addition to nodding, including side-to-side or rotary motions. They are typically pendular in character, and do not closely resemble epileptic spasms, which are more abrupt in onset and typically more irregular in occurrence. The rate of movement is typically 0.5 to 1 per second (30-60 per minute) in spasmus nutans, which is much more rapid than the maximum spasm rate of 13 per minute observed in infantile spasms patients (Kellaway et al., 1979). The presence of nystagmus, typically pendular or rotatory, is regularly associated with spasmus nutans, but can also be seen in symptomatic infantile spasms patients. The EEG reveals no abnormalities in association with the abnormal motor events in spasmus nutans (Kellaway and Glaze, 1982).

Lombroso and Fejerman (1977) described 16 patients with a disorder they designated **benign myoclonus of early infancy** which was characterized by motor spasms similar in appearance to those of infantile spasms. However, in all of these children the EEG was normal and the outcome was favorable whether the patients were treated or not. Developmental arrest or regression was not observed, the spasms ceased in all cases before the age of 2 years, and no other types of seizures appeared. The essential features of this syndrome have been confirmed in a number of subsequent investigations and case reports (Fejerman, 1984; Dravet et al., 1986; Donat and Wright, 1992; Ishida, 2000; Maydell et al., 2001). The clinical descriptions of most of these patients are entirely consistent with infantile spasms in terms of age of onset (typically within the first year of life), the character of the spasms (both flexor and extensor types, and involvement of head, neck, and limbs), the frequent occurrence of spasms in clusters, and the almost exclusive occurrence of spasms during wakefulness. However, unlike infantile spasms, the EEG is normal both ictally and interictally, and the prognosis is excellent, both for cessation of the spasms and for normal mental development. Pachatz et al. (1999) described 5 cases which they also diagnosed as benign myoclonus of early infancy, although the spasms were described as including shudder-like axial movements, in addition to more

typical tonic features. Unlike the other reports of this disorder, they felt that the events were triggered by excitement or frustration, and that clusters occurred only if there was persistence of the provoking state. Based upon the available information, it is clear that while this disorder is incompletely understood, and the pathophysiological basis unknown, it can present a clinical picture indistinguishable from that of recent onset cryptogenic infantile spasms. It can only be confirmed and differentiated from infantile spasms by the documentation of repeatedly normal ictal and interictal EEG findings in the continued presence of motor spasms.

2.3 Other medical conditions

Coulter and Allen (1982) described an entity present in several infants less than 1 month of age that was characterized by the occurrence of intermittent rhythmic myoclonic jerking of the limbs during sleep. Termed **benign neonatal sleep myoclonus**, this disorder has been confirmed in several additional studies (Dooley, 1984; Donat and Wright, 1992; Caraballo et al., 1998), and is associated with a benign course. Development is not impaired, and the condition typically resolves within a few months, although occasional cases with persistent symptoms have been described . Unlike sleep starts (see above, section 2.1), which typically occur only near the time of sleep onset, the myoclonic activity associated with this disorder can occur throughout the sleep period, although predominantly during early non-REM (quiet) sleep. The brief jerks usually are grouped in clusters of 4-5 events with intervals of around one second (American Sleep Disorders Association, 1997), although in some cases persistence for periods of several minutes at rates of 1 every 2-3 seconds has been reported (Coulter and Allen, 1982). The major clinical features differentiating this condition from infantile spasms are the very brief durations of the individual jerks, and the exclusive occurrence during sleep. This condition is not associated with abnormal EEG characteristics.

It is also relatively common for observers to attribute the ictal events associated with infantile spasms to manifestations of pain, especially that associated with **colic** (Druckman and Chao, 1955; Chao et al., 1957; Bower and Jeavons, 1959). In one study (Bellman, 1983) it was found that 15% of the cases eventually determined to be infantile spasms were initially diagnosed as colic by the child's physician. While individual events associated with a response to painful stimuli may closely resemble epileptic spasms, more prolonged and careful observation will usually allow such events to be properly distinguished: they will be more variable in character than spasms, which tend to be stereotyped, and will typically be associated with crying throughout the event, unlike spasms, which are rarely associated with crying during the ictal event (although crying may precede or follow the spasm).

In some infants with central nervous system damage isolated, or repetitive, **posturing** may occur spontaneously or with stimulation and may closely

resemble infantile spasms. However, these events are not associated with specific ictal EEG changes.

3. OTHER EPILEPTIC SYNDROMES

While infantile spasms (West syndrome) is recognized as a distinct entity in the International League Against Epilepsy (ILAE) Classification of Epileptic Syndromes (Commission, 1989), in clinical practice several other recognized entities can present diagnostic challenges, and, in some instances, clear-cut distinctions can not be made. Such problems have suggested to some investigators that several of the currently recognized epileptic syndromes may share a common pathophysiological basis, with the different clinical expressions reflecting primarily age-related maturational factors. Several of the epileptic syndromes discussed in this section fall into this category (early infantile epileptic encephalopathy, early myoclonic encephalopathy, Lennox-Gastaut syndrome), while others clearly do not (benign myoclonic epilepsy, severe myoclonic epilepsy, epilepsy with myoclonic-astatic seizures), even though they are associated with clinical characteristics that can sometimes be confused with infantile spasms. The similarities and distinguishing features of these epileptic syndromes, in comparison to infantile spasms, are reviewed below, and the most useful differentiating characteristics are summarized in Table 7.2.

3.1 Early infantile epileptic encephalopathy

Early infantile epileptic encephalopathy (EIEE), also known as Ohtahara's syndrome, is characterized by the onset of epileptic spasms in the neonatal period or within the first few months of life, a suppression-burst EEG pattern, a very poor prognosis both for mental development and seizure control, and high mortality. While it had been accepted for many years that infantile spasms can sometimes occur in the neonatal period, and that such cases are often associated with periodic, or suppression-burst, EEG patterns rather than typical hyps-arrhythmia (e.g., Hoefer et al., 1963; Lacy and Penry, 1976; see Chapter 5, section 2.2), it was proposed by Ohtahara et al. (1976) that such cases should be recognized as a separate syndrome. Ohtahara and his colleagues (Ohtahara et al, 1976, 1987a,b; Yamatogi and Ohtahara, 1981) have also argued that EIEE, infantile spasms, and the Lennox-Gastaut syndrome have many common features (including specific age dependencies, severe EEG abnormalities, similar etiological heterogeneity, frequent association with mental deficits, frequent refractoriness to therapy, and a grave prognosis) and, as a group, constitute a single age-dependent epileptic encephalopathy. Furthermore, transitions from EIEE to infantile spasms are common, as are transitions from infantile spasms to Lennox-Gastaut syndrome. Nevertheless, they felt that each of the three entities had sufficiently unique characteristics to warrant classification as individual syndromes.

Table 7.2 **Comparison of childhood epileptic syndromes: Typical or most common features.**

	EIEE	*EME*	*IS*	*LGS*	*BMEI*	*SMEI*	*EMAS*
Age of onset	0-3 m	0-3 m	3-8 m	1-8 y	1-2 y	3 m-7 y	7 m-10 y
Ictal events							
Epileptic (tonic) spasms	+++	+	+++	+	–	–	–
Tonic seizures	–	–	+	+++	–	+	+
Clonic seizures	–	–	+	+	–	+++	+
Tonic-clonic seizures	–	–	+	++	+	+	+
Myoclonic seizures	–	+++	+	+	+++	++	+++
Atonic seizures	–	–	–	+++	–	–	–
Absence seizures	–	–	–	+++	–	+	+
Partial seizures	++	++	++	++	–	++	–
Interictal EEG pattern							
Hypsarrhythmia	–	–	+++	–	–	–	–
Suppression-burst	+++	+++	+	–	–	–	–
Slow spike-wave	–	–	–	+++	–	–	–
Other abnormality	–	–	+	+	+	+++	+++
Normal	–	–	–	–	+++	–	–

+++ very common ++ common + occasional – rare or never

EIEE: Early infantile epileptic encephalopathy EME: Early myoclonic encephalopathy

IS: Infantile spasms LGS: Lennox-Gastaut syndrome

BMEI: Benign myoclonic epilepsy in infancy SMEI: Severe myoclonic epilepsy in infancy

EMAS: Epilepsy with myoclonic-astatic seizures

A number of subsequent studies have documented the essential features of EIEE in additional patients (Clarke et al., 1987; Lombroso, 1990; Martinez-Bermejo et al., 1995; Chakova, 1996; Wang et al., 1998; Chen et al., 2001; Itoh et al., 2001; Trinka et al., 2001), and several other reviews have provided critical assessments of the relationships between EIEE and infantile spasms (Aicardi, 1986, 1992; Donat, 1992; Kelley et al., 1999). Based on these reports, EIEE and

infantile spasms clearly share a number of basic features: Brief epileptic spasms are the most common seizure type, and can occur in an isolated manner, or in clusters. Associated etiological factors are diverse and similar in the two syndromes, and include a wide variety of brain malformations and various insults. Partial seizures are relatively common in both syndromes, in addition to spasms, and other seizure types can be seen as well in occasional cases. The characteristics that most clearly differentiate EIEE and infantile spasms are the following: The onset of EIEE is almost always within the first 3 months of life, and in most cases is within 30 days, while infantile spasms typically begins after 3 months of age, with a peak incidence at 4-6 months. The EEG exhibits a periodic suppression-burst pattern both awake and asleep in EIEE (paroxysmal bursts of irregular, high amplitude, slow activity mixed with spike and sharp wave complexes which persist for periods of several seconds, alternating with periods of markedly attenuated amplitude which persist for periods of 2-10 seconds), while the hypsarrhythmic pattern is characteristic in infantile spasms (see Chapter 5, section 2). While infantile spasms is sometimes associated with a suppression-burst pattern (as a variant of hypsarrhythmia), in such cases it is usually present only during nonREM sleep, unlike the pattern seen in EIEE which persists awake and asleep. It has also been observed by some investigators that the spasms associated with EIEE can occur both awake and asleep, while those seen in infantile spasms occur almost exclusively during wakefulness (Ohtahara et al., 1987b; Clarke et al., 1987).

Most investigators studying EIEE have noted that the syndrome is relatively unstable, and if the patient survives, there is often an evolution to infantile spasms or Lennox-Gastaut syndrome within a few months. In 3 studies which included more than 10 subjects each (range 11-15), an average of 71% (range 71-80%) of the survivors eventually exhibited a transition to infantile spasms, and several of those had a subsequent, much later, transition to the Lennox-Gastaut syndrome, while a few cases transitioned directly from EIEE to Lennox-Gastaut (Ohtahara et al., 1987b; Clarke et al., 1987; Chakova, 1996).

Based upon the limited information currently available, it is not clear whether or not EIEE should be classified as an independent syndrome. As noted above, many aspects of the disorder are identical to infantile spasms, and there is considerable overlap in all other areas except age of onset, which is itself an arbitrary distinction. It has been argued that this condition is more reasonably considered to be an early variant form of infantile spasms rather than a separate entity (Lombroso, 1990). We agree with the conclusion of Donat (1992) that this question can not be resolved until more precise and quantitative information regarding the characteristics of EIEE is made available through the use of EEG/video monitoring, as has been done in the case of infantile spasms (see Chapter 4). Although unresolved, this issue does not significantly impact clinical management since the therapeutic options available for EIEE are the same as those for infantile spasms.

3.2 Early (or neonatal) myoclonic encephalopathy

Early (or neonatal) myoclonic encephalopathy (EME) is characterized by the onset of myoclonic seizures (typically described as erratic or fragmentary myoclonus) within the first three months of life, a suppression-burst EEG pattern, severe neurological impairment, mental retardation, a high death rate, and a high incidence of other seizure types including partial seizures and epileptic spasms (Aicardi, 1986; Commission, 1989; Lombroso, 1990). In some cases the suppression-burst EEG pattern evolves, either transiently or permanently, to hypsarrhythmia, resulting in a clinical picture consistent with infantile spasms (Commission, 1989; Ohtahara et al., 1997; Yelin et al., 1999; Chen et al., 2001). Thus, EME shares a number of characteristics with both EIEE and infantile spasms, such as overlapping onset ages and EEG features, and in clinical practice it may sometimes be very difficult, or impossible, to determine which of these entities best matches a particular case.

The key differentiating feature of EME, in comparison to both infantile spasms and EIEE, is the major seizure type. While infantile spasms and EIEE are most frequently associated with epileptic spasms, these events are usually absent initially in EME, although they often occur later in the course of the disorder. The most common seizure type in EME is usually said to be "erratic" and/or "fragmentary" myoclonus, and most investigators have provided no further characterization of the ictal events (Aicardi, 1986; Otani et al., 1989; Lombroso, 1990; Kelley, et al., 1999; Chen et al., 2001). In particular, there have been no quantitative descriptions which permit a careful distinction of these events from those characteristic of infantile spasms and other syndromes (Donat, 1992). In one of the few studies to provide any detail of the myoclonic movements associated with EME, Ohtahara et al. (1997) observed that frequently there was only slight twitching of the distal ends of the extremities, the eyelids, or the corners of the mouth, although occasionally 'massive myoclonus' was present. These investigators also observed that the myoclonic movements often could be very subtle. Thus, based on the very limited information available, the primary ictal events in EME apparently are much shorter in duration and are more variable (i.e., less stereotyped) than the corresponding seizures of EIEE and infantile spasms.

The suppression-burst EEG pattern characteristic of EME has been reported to be somewhat less persistent than that seen in EIEE, sometimes appearing primarily, or exclusively during sleep (Ohtahara et al., 1997; Kelley et al., 1999; Chen et al., 2001). In such cases, the EEG pattern would be consistent with the variant of hypsarrhythmia associated with episodes of voltage attenuation seen in some infantile spasms patients (see Chapter 5, section 2.1). Consequently, the EEG characteristics are of limited value in the differential diagnosis.

The etiological associations of EME clearly overlap those of both infantile spasms and EIEE. However, it has been reported that, in comparison to EIEE, EME is more likely to be cryptogenic, or associated with genetic (particularly

metabolic) disorders, as contrasted with a higher incidence of structural abnormalities and cerebral insults in EIEE (Aicardi, 1986; Otani et al., 1989; Lombroso, 1990; Ohtahara et al., 1997; Wang et al., 1998; Chen et al., 2001). But, since the etiological factors associated with infantile spasms clearly overlap both EIAA and EME (see Chapter 9), such considerations are of no significant value in distinguishing infantile spasms from these disorders.

As with EIEE, the true nosological status of EME is still unclear. There is a great deal of overlap between EME and EIEE, and it has been suggested that they are the same entity (Yelin et al., 1999). Likewise, there is much similarity with infantile spasms, and both EME and EIEE sometimes exhibit an evolution to the former syndrome. More precise characterization of these entities is needed in order to clarify the interrelationships and to permit a more meaningful classification scheme.

3.3 Lennox-Gastaut syndrome

The Lennox-Gastaut syndrome (LGS) is a seizure disorder with onset in childhood (typically between 1-8 years of age) characterized by a variety of seizure types, an abnormal background EEG pattern with 1.0-2.5 Hz slow spike-wave activity, and, usually, severe developmental delay (Lennox and Davis, 1950; Gastaut et al., 1966; Markand, 1977; Weinmann, 1988; Commission, 1989). In this disorder, tonic, atonic (often associated with head drops and falling episodes), and absence seizures are the most typical, although generalized tonic-clonic and partial seizures are not uncommon. A relationship between LGS and infantile spasms has long been recognized since it is not unusual for patients with classical infantile spasms to exhibit an evolution to LGS within months or years. As discussed in Chapter 12 (section 6), based on a review of 15 studies which evaluated the long-term prognosis of infantile spasms patients, an average of 17% eventually developed LGS. It has also been observed that around one third of patients with LGS have a history of infantile spasms and/or hypsarrhythmia (Niedermeyer, 1969; Ohtahara et al., 1976; Trevathan et al., 1997; Hoffmann-Riem et al., 2000).

The diagnostic features of typical LGS are relatively clear-cut, and not likely to be confused with infantile spasms, especially when the onset is beyond 12 months of age, and the slow spike-wave EEG pattern is continuously present. The tonic seizures of LGS are more prolonged than the epileptic spasms of infantile spasms, which typically last no more than a few seconds and often occur in clusters. However, it must be realized that brief epileptic spasms can be seen in LGS (although they only rarely occur in series), while more prolonged tonic seizures occasionally are seen in infantile spasms (Kurokawa et al., 1980; Donat and Wright, 1991c).

The differential diagnosis can be more difficult later in the course of infantile spasms, or when onset is beyond one year. In such instances, the EEG characteristics may be less helpful (Bednarek et al., 1998), and in some cases

there may be clinical and electroencephalographic features consistent with both infantile spasms and LGS. As discussed above (section 3.1) it has been suggested that infantile spasms and LGS, together with EIEE, represent a continuum, or evolutionary process, which may reflect a common underlying pathophysiological process. If so, transitional forms are to be expected and may simply reflect the interaction of normal maturational processes within a pathological substrate.

3.4 Benign myoclonic epilepsy in infancy

Benign myoclonic epilepsy in infancy (BMEI) occurs during the first or second years of life in previously normal children, many of whom have a family history of epilepsy, and sometimes follows a febrile seizure (Lombroso, 1990; Commission, 1989; Fejerman, 1994). The seizures are described as consisting of brief bursts of generalized myoclonus associated electroencephalographically with generalized spike-wave bursts, and occur during the early stages of sleep. While the seizures are readily controlled by medical therapy, a tendency for the occurrence of generalized tonic-clonic seizures in adolescence has been reported. BMEI is sometimes accompanied by cognitive or personality disorders.

BMEI has been confused with infantile spasms on the basis of clinical history, although it can be readily differentiated from the latter by EEG/video monitoring (Donat and Wright, 1992). In particular the brief, myoclonic character of the ictal events and the accompanying spike-wave EEG pattern are inconsistent with infantile spasms, as is the typical occurrence during sleep.

3.5 Severe myoclonic epilepsy in infancy

Severe myoclonic epilepsy in infancy (SMEI) typically begins between 4 and 12 months of age in previously normal children and often follows a prolonged febrile seizure. Patients with SMEI frequently have a family history of seizures. Generalized or unilateral clonic seizures which can be precipitated by fever are seen initially, and are associated with generalized spike or polyspike and wave electroencephalographic patterns (Ogino et al., 1988; Commission, 1989; Lombroso, 1990). Other seizure types (generalized tonic-clonic, partial, and myoclonic jerks) often follow within months or years and are typically refractory to medical therapy. This condition is typically associated with mental retardation after onset, and other neurological deficits are common. As with BMEI, this disorder may initially be confused with infantile spasms, but can readily be distinguished by the EEG findings and characteristics of the seizures.

3.6 Epilepsy with myoclonic-astatic seizures

Epilepsy with myoclonic-astatic seizures (EMAS) is typically associated with brief myoclonic seizures which may involve limbs, neck, face and/or axial

musculature, and which may result in flexion of the body sufficient to produce a fall (Fejerman, 1994). Onset is between 7 months and 10 years, and most children are developmentally normal prior to onset (Commission, 1989; Fejerman, 1994). The interictal EEG is abnormal and may show high amplitude 4-7 Hz activity as well as generalized spike or polyspike-wave activity (Fejerman, 1994). It is possible that the flexor character of the ictal events could result in misinterpretation of EMAS as epileptic spasms by an observer, but the use of EEG/video monitoring should allow a correct interpretation based on the rapidity of the movements, and the absence of ictal or interictal EEG features typical of infantile spasms.

4. SUMMARY AND SYNTHESIS

Infantile spasms can be confused with a variety of other phenomena of both normal and abnormal character. The brief, transitory character of spasms makes it very difficult for parents and other observers to provide an accurate description of the events, and there is a tendency to interpret these abnormal movements initially as normal infant behavior. Consequently, they may be dismissed as Moro reflexes, other startle responses, sleep starts, rhythmic movements such as headbanging or rocking during sleep or drowsiness, and various other infant motor activity. In other cases, there may be confusion with other medical conditions of a non-epileptic character, such as spasmus nutans, benign myoclonus of early infancy, benign neonatal sleep myoclonus, and colic. In most instances an electroencephalogram is necessary in order to confirm the presence of an epileptic disorder, and in many cases combined EEG/video monitoring will be required in order to clearly differentiate infantile spasms from these other entities.

It is usually more difficult to differentiate infantile spasms from other epileptic syndromes. Early infantile epileptic encephalopathy, or Ohtahara's syndrome, for example, has characteristics that often overlap with those of infantile spasms, and differs primarily by an earlier age of onset. Early myoclonic encephalopathy also can present a diagnostic challenge, with features that can be difficult to distinguish from those of both infantile spasms and EIEE, although careful documentation of the ictal events usually permits differentiation. Both EIEE and EME sometimes exhibit an evolution to infantile spasms. The Lennox-Gastaut syndrome also shares many characteristics with infantile spasms, although its later onset and characteristic EEG pattern usually facilitate diagnosis. However, infantile spasms often exhibits an evolution to LGS after variable lengths of time, and consequently transitional forms with features of both disorders may be seen.

Several other epileptic syndromes of infancy and childhood can, at times, be confused with infantile spasms, including benign myoclonic epilepsy in infancy, severe myoclonic epilepsy in infancy, and epilepsy with myoclonic-astatic seizures. In these instances EEG/video monitoring will effectively provide

adequate information to permit correct differentiation from infantile spasms in essentially all cases.

5. FUTURE RESEARCH

The relationships between infantile spasms, early infantile epileptic encephalopathy (EIEE), early myoclonic encephalopathy (EME), and Lennox-Gastaut syndrome (LGS) are currently poorly understood, and consequently, as discussed above, these entities often are confused diagnostically. While all of these conditions are recognized as independent syndromes in the current Classification of Epileptic Syndromes (Commission, 1989), there clearly are many common features that suggest the possibility that they share a single underlying pathophysiological process (or processes). For example, many clear-cut cases of EIEE, and some cases of EME, eventually, within weeks or months, exhibit a gradual transformation of EEG patterns and seizure characteristics so that they eventually assume a diagnostic pattern entirely consistent with infantile spasms. Similarly, a significant proportion of patients diagnosed as infantile spasms during the first year of life, gradually evolve over months, or even years, to assume a clinical picture entirely consistent with LGS. It has been suggested that this transitional process is evidence for underlying similarity of pathological mechanisms, and that the interaction of normal maturational processes with the underlying pathology is responsible for the differing clinical expression over time. But, if this is the case, it is then difficult to explain why not all patients with EIEE or EME go on to develop infantile spasms and why not all infantile spasms patients develop LGS. Instead, it may suggest that these entities are indeed independent, and reflect different underlying pathological processes. Under some circumstances it is possible for one pathological mechanism to trigger, or induce, a second, independent process. Clarification of these issues is a basic prerequisite to the development of improved therapeutic regimens for these disorders. For example, if EIEE, infantile spasms, and LGS result from different mechanisms, then it might be possible to prevent evolution to infantile spasms from EIEE, or LGS from infantile spasms by early therapeutic intervention of a specific type, and possibly improve the prognostic outlook.

Chapter 8

Relationship to Other Seizure Types

1. INTRODUCTION

The characteristic seizure in infantile spasms is the epileptic spasm, which consists of a sudden muscular contraction of variable duration which usually involves both axial and extremity musculature, and which can occur singly or as clusters containing multiple events. These seizures, which are considered to be generalized, are typically biphasic, with an initial rapid component lasting no longer than 2 seconds, and a subsequent tonic component which persists for 2-10 seconds, and can assume a wide variety of clinical patterns (see Chapter 4, section 3.2). Infantile spasms can, however, be associated with a number of other seizure types of both partial and generalized origin. For example, seizures of other types may precede the onset of infantile spasms by weeks, or even months, in which case they often reflect underlying pathological factors, such as pre- and perinatal insults, brain malformations, and metabolic abnormalities. In other cases such seizures occur only after the onset of infantile spasms, and may then occur concurrently with spasms for months, or years, often persisting even when the spasms are controlled by medical therapy. In still other instances, seizures of various types appear only after spasms have ceased, and may be a continuing problem for many years. The total number of infantile spasms patients who experience other types of seizures at some time (either before spasm onset, during the time spasms are present, or after spasm cessation) has been reported to be in the 40-50% range (Hoefer et al., 1963; Jeavons and Bower, 1964; Koo et al., 1993). In this chapter the various seizure types that can be associated with infantile spasms are reviewed, and the patterns of occurrence are discussed with respect to etiology and possible pathophysiological mechanisms. This topic is also addressed in Chapter 12, section 3.3, where evidence that the presence of other seizure types is an unfavorable prognostic indicator is reviewed.

2. SEIZURES PRECEDING SPASM ONSET

Seizures of other types precede the onset of infantile spasms in a significant number of cases. In 10 studies of unselected infantile spasms patients, with group sizes of 25-698 subjects each, an average of 19% of the patients (range 7-46%) had experienced seizures of some type prior to the onset of spasms (Druckman and Chao, 1955; Livingston et al., 1958; Jeavons and Bower, 1964; Volzke et al., 1967; Seki et al., 1976; Anandam, 1983; Velez et al., 1990; Wang et al., 1994; Okumura et al., 1998; Kubota et al., 1999). In these studies, the seizures documented before the onset of spasms were of many different types, and included various neonatal seizures, generalized tonic, clonic, tonic-clonic, myoclonic, and partial seizures.

The timing of other seizure types with respect to the onset of infantile spasms also varies considerably. For example, following neonatal seizures there may be a seizure free interval of several months before the onset of spasms (Clancy and Legido, 1991; Rantala et al., 1996). In other cases seizures characteristic of a specific neonatal epileptic syndrome (e.g., early infantile epileptic encephalopathy or early myoclonic epilepsy) may exhibit a gradual evolution, or transition, to infantile spasms over time (see Chapter 7, section 3). In still other cases, seizure-free since birth, partial or generalized seizures may begin after several weeks or months, and continue to occur for several additional weeks, or months, before the eventual onset of infantile spasms (Velez et al., 1990; Okumura et al., 1998). Velez et al. (1990) observed that infantile spasms tended to occur sooner (average delay approximately 1.5 months) after the onset of other seizure types in patients with etiological factors classified as prenatal (malformations, genetic disorders), in comparison to those patients with peri- and post-natal insults (average delay nearly 6 months).

3. SEIZURES CONCURRENT WITH SPASMS

3.1 Incidence and seizure types

The other seizure types that begin prior to the onset of infantile spasms (section 2, above) often continue after spasm onset, and, in addition, other seizures frequently occur for the first time in patients in whom spasms are already present. In 5 studies of unselected infantile spasms patients, with group sizes of 25-698 subjects each, an average of 25% of the patients (range 8-42%) had other seizures during at least a portion of the time that spasms were present (Druckman and Chao, 1955; Livingston et al., 1958; Jeavons and Bower, 1964; Seki et al., 1976; Kurokawa et al., 1980; Gaily et al., 1995). The specific seizures observed in these studies included both partial and generalized (tonic, tonic-clonic, atonic, myoclonic, and atypical absence) types. As would be expected, it has been documented that those patients classified as symptomatic are more likely to develop other concurrent seizure types than are children in the

cryptogenic category (Riikonen and Simell, 1990; Koo et al., 1993; Lortie et al., 1997).

3.2 Coupling of spasms and other seizures

In most cases, other types of seizures that occur in infantile spasms patients appear to be independent of epileptic spasms, and apparently simply reflect underlying pathological factors, which are often multiple. However, occasionally, epileptic spasms occur simultaneously with, or in close temporal relationship to, other types of seizures. For example, we (Hrachovy et al., 1984) observed that in some patients exhibiting the hypsarrhythmic variant pattern associated with a consistent focus of abnormal discharge (see Chapter 5, section 2.1), focal electrical seizure discharges, sometimes associated clinically with partial seizures, could occur during a cluster of spasms. In these cases, the focal discharges did not appear to modify the ictal complexes associated with epileptic spasms, nor was the clinical appearance of the spasms noticeably modified. In such cases, the possibility exists that there may in fact be some common element causing, or triggering, both epileptic processes, although it could also simply reflect a chance coincidence. Subsequently, a number of investigators reported similar observations and suggested that the coupling of partial seizures with spasms supported the hypothesis that infantile spasms occur as a result of an interaction between cortical and subcortical structures (see Chapter 10).

Bour et al. (1986) observed partial seizures preceding or during clusters of spasms in all of 7 patients with Aicardi syndrome studied during long duration EEG monitoring, and concluded that this relationship suggested a common origin for both seizure types. Subsequently, Yamamoto et al. (1988) described 4 cases of infantile spasms in which clusters of spasms were regularly preceded by a partial seizure, which ceased 10-25 seconds before onset of the first spasm. This relationship was initially reported by parental observation, and was confirmed during EEG/video monitoring studies in all patients. These investigators suggested that in these cases the cortical partial seizure discharges may have triggered, or stimulated, abnormal brainstem structures to produce the generalized epileptic spasms. Donat and Wright (1991b) reported an additional 11 cases in which partial seizures were coupled to spasms. In this study a somewhat different pattern of occurrence was observed, with 7 subjects having a partial seizure preceding onset of a spasm cluster, but with persistence of the partial seizure into the initial portion of the cluster, and overlapping with one or more spasms. In the other 5 cases a partial seizure occurred immediately following a spasm and ended prior to the next spasm of the cluster. It was noted that these patients also had some partial seizures that were not associated with spasms, and spasms not coupled to partial seizures, although a quantitative analysis of the relationship was not provided. These investigators felt that the first pattern could reflect a mechanism similar to that proposed by Yamamoto et al. (1988, see above) in which the partial seizure lowers the brainstem threshold

for spasm generation, although the possibility of a coincidental relationship was also recognized (see Chapter 10, section 3.2). The second pattern, in which a spasm often preceded a partial seizure, suggested, instead, that the primary occurrence of a spasm might produce enhanced excitability in cortical foci with the resultant initiation of a focal seizure at that site.

This apparent coupling of epileptic spasms and partial seizures in some infantile spasms patients has been documented in a number of subsequent studies (Carrazana et al., 1993; Plouin et al., 1993; Viani et al., 1994b; Donat and Lo, 1994; Hrachovy et al., 1994a; Gaily et al., 1995; Haga et al., 1995a; Ohtsuka et al., 1996, 1998; Kubota et al., 1999; Toribe et al., 2001; Yoshioka et al., 2001), and, as in the earlier studies, various relationships have been observed, with spasm clusters sometimes following cessation of partial seizures, sometimes occurring during partial seizures, and partial seizures occasionally following spasms. In spite of the considerable interest in this phenomenon, it is still not clear how frequently it occurs, with most of the studies simply reporting specific cases selected for the association. In 6 studies of unselected infantile spasms patients (with group sizes of 42-96 subjects each) which did provide such information the reported proportion of patients who exhibited apparent coupling of partial seizures and spasms varied widely from as low as 5% to as high as 38%, with an average across all studies of 21% (Plouin et al., 1993; Hrachovy et al., 1994a; Gaily et al., 1995; Haga et al., 1995a; Ohtsuka et al., 1996; Kubota et al., 1999). Our study (Hrachovy et al., 1994a) reported the lowest value, with only 5 of 96 patients (5%) exhibiting apparent coupling of spasms and partial seizures during prolonged EEG/video monitoring studies. In addition, in only 3 subjects (3%) was the coupling effect shown to be statistically significant. The reason for the marked differences in the results of these studies is unknown, but is undoubtedly related to differences in experimental design. Most studies did not provide precise criteria by which the presence of coupling was determined, and in only one investigation were the results analyzed statistically to assess the possibility of coincidental associations.

We have also occasionally observed that clusters of epileptic spasms in infantile spasms patients can be preceded by tonic seizures (Hrachovy, 2001). Tonic seizures, as opposed to epileptic spasms, lack the initial phasic component (see Chapter 5), and are more prolonged. In a series of 57 patients with infantile spasms 3 (5%) had an apparent coupling of these two seizure types, suggesting that both tonic seizures and epileptic spasms may be generated by the same mechanism.

4. SEIZURES FOLLOWING CESSATION OF SPASMS

When patients with infantile spasms are followed for long periods of time it is clear that, while epileptic spasms almost always cease within a few years, whether initial treatment is successful or not, other seizure types are common and often persistent. In a large number of studies in which the minimum follow-

up period averaged 2 ½ years (see Chapter 12, section 4.1) an average of 51% of the patients were continuing to experience seizures, most of which were of types other than epileptic spasms. The specific seizures reported in these patients encompass essentially all types of partial and generalized seizures. The most common seizure type observed during long-term follow-up has varied considerably across studies. Generalized seizures have been reported to be the most frequent type in a number of studies, including, specifically, tonic-clonic seizures (Jeavons et al., 1973; Seki et al., 1976), astatic/akinetic (Taylor, 1952), myoclonic (Wang et al., 1994), or unspecified generalized (Druckman and Chao, 1955; Okumura et al., 1998). Other investigators have found partial seizures (with or without secondary generalization) to be the most common (Cavazzuti et al., 1984; Curatolo et al., 1986; Riikonen and Amnell, 1981; Iinuma, 1999; Kankirawatana et al., 2002). The observed diversity in the most common types of seizures observed in these groups of patients is probably largely due to the variability in the follow-up periods for individual patients. Hughes et al. (1997) analyzed long-term changes in 505 patients with infantile spasms, some of whom were followed for as long as 43 years. They observed an age dependency among the various seizure types seen in these patients: Generalized tonic-clonic seizures were infrequent in subjects less than 3 years old, but the incidence increased thereafter to a peak in the early 20s, when they were present in 63% of the patients. Complex partial seizures were rare below 8 years of age, and reached a peak incidence of approximately 50% by age 40 years. The lowest incidence of seizures was seen at 9 years of age, when 53% of the subjects were seizure-free.

5. SUMMARY AND SYNTHESIS

Patients with infantile spasms often exhibit other seizure types in addition to epileptic spasms during the course of the disorder. Other types of seizures may precede the onset of spasms and/or occur concurrently with spasms. They may persist after spasms have stopped, or may appear for the first time after cessation of spasms. Essentially any type of seizure can be seen at these times, including both generalized and partial forms, and are more common in symptomatic patients.

While most seizures of other types that occur in infantile spasms patients are independent of epileptic spasms, and most likely reflect the diversity of underlying pathology present in many instances, in a subset of cases there is sometimes an apparent coupling of partial seizures and epileptic spasms. Partial seizures are seen immediately preceding spasm clusters in some instances, but may occur during clusters or immediately following spasms. This phenomenon has been thought by many investigators to support the hypothesis that infantile spasms is based on a pathophysiological mechanism involving specific interactions of cortical and subcortical (probably brainstem) structures.

6. FUTURE RESEARCH

The relationship between epileptic spasms, the most characteristic ictal manifestation of infantile spasms, and other seizure types that also frequently occur in this disorder is still poorly understood. As discussed above, the fact that, at least in some cases, there is a temporal relationship between spasms and partial seizures has important implications for hypotheses regarding the pathophysiological basis of infantile spasms (see Chapter 10). If coupling of these seizure types is relatively common, as some studies have suggested, it clearly strengthens the hypothesis that infantile spasms may be dependent on an interaction of cortical and subcortical mechanisms. However, the evidence for this coupling is still sparse since most investigations have not been quantitative in character, and have not provided clear definitions of what is required to substantiate a temporal relationship between different seizure types in a specific patient. Further studies are needed in order to clarify this relationship and to determine with statistical validity the extent to which true coupling of seizure types occurs.

In addition, most prior studies of the temporal relationships existing between epileptic spasms and other seizure have focused on partial seizures, since these events have often been apparent to observers. However, preliminary evidence exists that similar coupling may occur in the case of some tonic seizures and spasms. Consequently, additional information of importance to the further understanding of the underlying basis of infantile spasms could be derived from well-designed studies which apply appropriate statistical methods to the determination of time relationships existing between epileptic spasms and all other seizure types seen in an individual infantile spasms patient.

Chapter 9

Etiology and Pathology

1. INTRODUCTION

The basic, or fundamental, cause of infantile spasms is unknown. It has been recognized for many years that children who have some degree of preexisting central nervous system dysfunction are at increased risk for developing this disorder within the first year of life. But, this is not invariably true, and a significant number of cases occur in children who have apparently developed normally until the time of onset. In this chapter, we consider the vast number of pathological conditions that have been identified as probable, or possible, etiological and predisposing factors. In most instances, it is not possible to determine with any degree of certainty whether or not a particular condition is causally related to the onset of infantile spasms, as opposed to simply coincidental. These issues are addressed again in Chapter 10, where evidence concerning the pathophysiological basis of the disorder is considered.

2. CLASSIFICATION

Because of the wide range of pathological conditions that appear to be associated with infantile spasms, investigators have typically attempted to categorize patients with this disorder in order to maximize the chances of detecting features of potential value in determining the best course of therapy, and for refining prognostic indicators. Several classification schemes have been used, and have proven to be useful in the management of this disorder.

2.1 Idiopathic, cryptogenic and symptomatic

The most fundamental classification scheme based on etiology encompasses two broad categories: an idiopathic group and a symptomatic group. The

symptomatic group includes all patients with infantile spasms in whom a probable etiological or predisposing factor can be identified (e.g., congenital anomalies, history of prenatal complications or birth trauma, CNS infections, CT/MRI abnormalities, etc.), while the idiopathic group includes all other cases. Many early, and most subsequent, investigators have also recognized a cryptogenic category, which Lacy and Penry (1976) include as a subdivision of the idiopathic group. They defined this group as including all patients without evident etiological factors, and who also have exhibited normal development from birth until the onset of infantile spasms (patients in this category may, however, show developmental arrest subsequent to onset of the disorder). The distinction between cryptogenic and idiopathic is conceptual, with 'cryptogenic' denoting an uncertainty regarding the underlying cause, and leaving open the possibility that a specific etiological factor exists, but is not evident. The situation has been additionally complicated by the use of the term "doubtful" by some investigators' (e.g., Jeavons and Bower, 1960; Jeavons et al., 1970), to denote patients with abnormal development prior to onset of infantile spasms, but with no identifiable specific etiological factor. The 'doubtful' category has been considered by some investigators to be a subdivision of the idiopathic group (Lacy and Penry, 1976), but has been included within the symptomatic group by others (Jeavons and Bowers, 1960). In more recent years, however, few investigators have followed this tripartite classification scheme, and most have simply included the doubtful cases in the symptomatic category, taking the point of view that if development has been abnormal prior to onset, an underlying pathological process clearly has been present. These investigators have usually classified all other cases (with normal development, an absence of clinical etiological factors, and normal brain imaging studies) as cryptogenic. Thus, most investigators have used the term 'idiopathic' synonymously with 'cryptogenic' - i.e., to indicate patients with normal prior development and an absence of evident etiological factors.

More recently, some investigators have proposed that the terms 'idiopathic' and 'cryptogenic' should be used according to the original Greek meanings, with idiopathic signifying a disease produced by itself, with no other cause, and without brain damage (i.e., a purely functional disorder), and cryptogenic referring to cases with presumed underlying causal factors which remain hidden. It is argued that under this definition both cryptogenic and idiopathic infantile spasms cases are characterized clinically by normal development prior to onset, symmetrical spasms, no evidence of a brain lesion (by clinical, EEG, or imaging techniques), and no recognizable cause (see review by Dulac and Plouin, 1994). However, according to this proposal, the cryptogenic cases will later exhibit evidence of persistent brain dysfunction, while the idiopathic cases eventually recover completely with no residual brain dysfunction. While this definition is based on the ultimate outcome, and can not be confirmed with certainty at the time of diagnosis on the basis of history and presenting features, it is further argued that the idiopathic cases can be differentiated by disappearance of EEG

spikes after IV diazepam and reappearance of hypsarrhythmia between consecutive spasms of a cluster (Dulac et al., 1986b; see also Chapter 12, section 3.3). The cryptogenic cases, under this definition, are likely to show a persistent focus after IV diazepam and an absence of hypsarrhythmia between spasms (Dulac and Plouin, 1994). This concept is also supported by the work of Kasai et al. (1995), who found, through the use of serial MRI studies, that more than half of 9 patients originally classified as idiopathic (cryptogenic) exhibited delayed myelination later (typically by 7-12 months of age). The above studies are of great interest and perfection of this approach could significantly improve the ability to classify patients with respect to outcome measures.

Because of the above noted inconsistencies in the use of the terms cryptogenic and idiopathic the reader must carefully consider the specific criteria used in each study before assuming that results of various investigations can be safely compared. In the remainder of this chapter, and elsewhere in this book, unless otherwise specified, we will use the term cryptogenic to indicate all patients with normal prior development, no evident etiological factors, and normal imaging studies, and use the term symptomatic to include all patients not meeting the cryptogenic criteria.

In our review of this subject, we identified 65 published studies (see Appendix 1-A) in which information was provided regarding the relative numbers of cryptogenic and symptomatic patients (studies were excluded if they included fewer than 25 subjects, or if they were restricted to specific etiological or diagnostic categories). The number of reported cryptogenic patients was highly variable across studies, ranging from as low as 3% (Aydinli et al., 1998) to as high as 66% (Bellman, 1983), with an average value of 28%. There appear to be two major reasons for the extreme variability of this measure: Inconsistent criteria for deciding the presence of an etiological factor, and improvement in diagnostic techniques over time.

The first of these reasons is difficult to quantify since the exact criteria for concluding that a particular patient falls into the symptomatic category are not provided in most studies. However, consideration of specific etiological factors listed in some studies (see Section 3, below) makes it clear that this process is highly subjective. For example, some investigators have attributed specific cases to such factors as fever of unknown origin, premature rupture of membranes, and maternal diabetes, while these factors are not mentioned in some other large series. It seems likely that some physicians hesitate to make a causal association in the absence of evidence that a particular factor actually resulted in neurological impairment prior to onset of infantile spasms, while others feel that any atypical event or condition in the patient's history should be identified as a potential predisposing factor. These may be honest differences of opinion, but clearly contribute to the observed variability.

The other major reason for the observed variability in the ratio of cryptogenic to symptomatic cases is the continual improvement in diagnostic capability which has occurred over the years. Brain malformations and other lesions

which are readily identified with current CT and MRI techniques were frequently not detectable using the limited x-ray and pneumoencephalographic methodologies available 30-50 years ago. Consequently, it is to be expected that many patients presently categorized as symptomatic on the basis of clearly documented central nervous system structural abnormalities would have been considered cryptogenic in earlier studies. PET has recently added another level of sensitivity, and focal areas of metabolic dysfunction have been demonstrated in many infantile spasms patients that would otherwise be classified as cryptogenic on the basis of clinical, CT, and MRI findings (Chugani and Conti, 1996). The effect of this diagnostic evolution is apparent in Fig. 9.1, in which the data from the 65 studies included in Appendix 1-A are plotted with respect to the year of publication. In spite of the variability inherent in the data, the regression line reveals a clear downward trend in the percentage of patients classified as cryptogenic over the 50 year time span, from around 50% in the 1950s to a current (2002) value of approximately 20 %. In other words, with current diagnostic capability approximately 80% of infantile spasms cases can be associated with a potential etiological factor.

This classification scheme has proven to have significant practical value in the management of infantile spasms. As discussed in Chapter 12, the single most favorable prognostic indicator, for seizure control as well as for developmental outcome, is classification into the cryptogenic category at the time of initial diagnosis.

2.2 Pre-, peri-, and post-natal associations

Symptomatic cases have often been further subclassified on the basis of the presumed etiological factor's temporal relationship to the time of the patient's birth. Investigators have, thus, frequently grouped such cases into prenatal, perinatal, and postnatal categories based on an estimation of the time of occurrence of the cerebral insult. The results of this type of classification are illustrated in Table 9.1, which provides the percentage of symptomatic patients assigned to each of the three categories in 16 relatively large studies (with study populations ranging from 32 to 469 symptomatic patients). It is evident from this example that the results of such efforts are extremely variable. On average, more patients in these studies were classified into the prenatal group (40%), followed by the perinatal group (33%), with relatively few patients classified as postnatal (12%). However, the distribution of cases is not consistent across studies, and there is a wide range of values within each group. In the prenatal category, the proportion of patients ranged from a low of 15% (Rating et al., 1987) to a high of 79% (Wong, 2001), while in the perinatal category values from 7% (Ohtsuka et al., 2000) to 76% (Chakova et al., 1998) were documented. Postnatal patients were least frequent in the majority of these studies, although values ranged from 3% (Chakova et al., 1998) to 32% (Curatolo et al., 1981).

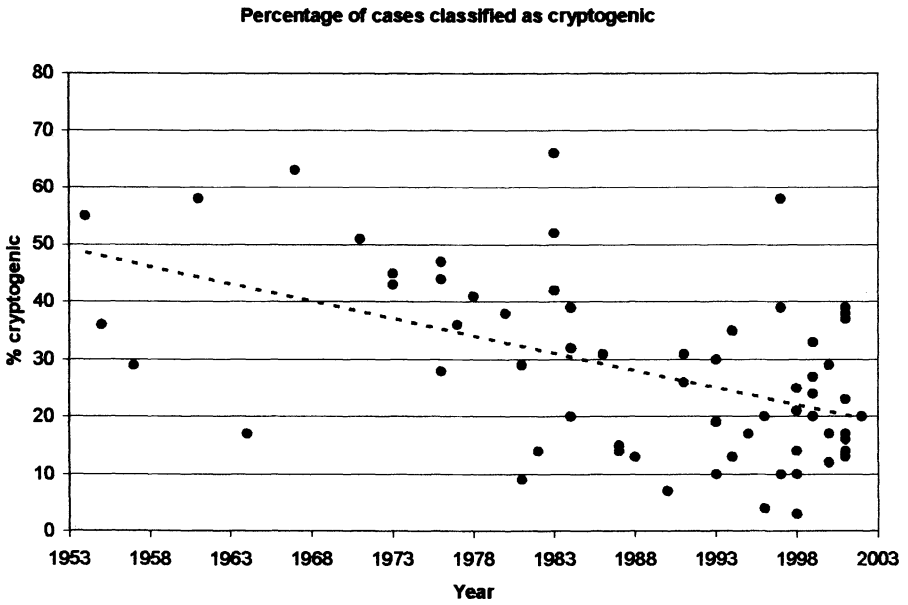

Figure 9.1 Reported percentage of infantile spasms patients classified as cryptogenic in 65 studies. Values plotted by date of publication. Studies with fewer than 25 cases were not included. Studies were also excluded if the population was preselected by etiological, diagnostic or outcome variables. Patients originally classified as symptomatic solely on the basis of preceding immunization were included in the cryptogenic group in this illustration, whenever possible. The dashed trendline displays the results of linear regression analysis, and suggests that the number of patients classified as cryptogenic has tended to decline over the past 50 years, presumably reflecting improved diagnostic techniques. References provided in Appendix 1-A.

The reason for the marked variability of the classification results across studies is probably the inherently subjective nature of the decision process. Some factors are clear-cut, and are likely to be classified uniformly by most investigators. For example, uterine hemorrhage, congenital infections, maternal toxemia, and genetic disorders are all clearly prenatal in origin, birth trauma is unquestionably perinatal, and meningitis or encephalitis occurring at several months of age is definitely postnatal. But, in many other cases it is very difficult, or even impossible, to determine with certainty when an insult resulting in brain damage actually occurred, particularly in terms of differentiating prenatal from perinatal causes. For example, as Jeavons and Bower (1964) pointed out 38 years ago, a history of difficulty in resuscitation following birth could signify a perinatal origin (such as intracranial hemorrhage during delivery), but could also be a result of various prenatal factors (intrauterine anoxia, malformations, etc). Differentiating among such possibilities at the time of infantile spasms onset, when the patient may be several months old, may be impossible.

Because of the difficulties inherent in this classification scheme, it has not proven to be of significant value in the management of infantile spasms, or in

Table 9.1
Pre-, peri-, and postnatal classification of symptomatic patients*

		% of symptomatic group			
	Number of patients	*Prenatal*	*Perinatal*	*Postnatal*	*Unknown*
Bellman (1983)	92	39	52	9	
Chakova et al. (1998)	42	21	76	3	
Curatolo et al. (1981)	57	23	46	32	
Druckman and Chao (1955)	47	32	38	30	
Haga et al. (1995b)	35	46	14	6	34
Kurokawa et al. (1980)	469	37	26	12	25
Matsumoto et al. (1981c)	182	40	24	9	26
Matsuo et al. (2001a,b)	39	56	15	5	**
Ohtahara et al. (1993)	162	48	15	7	30
Ohtsuka et al. (2000)	168	52	7	7	34
Rating et al. (1987)	39	15	41	13	31
Siemes et al. (1984)	41	51	32	5	12
Walther et al. (1987)	101	28	56	14	
Watanabe et al. (1982)	32	53	25	7	
Watanabe et al. (1987)	42	24	52	24	
Wong (2001)	38	79	11	11	
Average:	99	40%	33%	12%	
Minimum:	32	15%	7%	3%	
Maximum:	469	79%	76%	32%	

* Studies with fewer than 25 subjects excluded

** 23% were in "low birth weight" category

assessing prognosis or the probabilities for successful treatment. The available findings do, however, suggest that the vast majority of infantile spasms cases follow insults that occur very early in life (pre- and peri-natal periods), and that postnatal factors are relatively infrequent.

3. SPECIFIC ETIOLOGICAL FACTORS

3.1 General considerations

In our review of more than 400 published studies (Appendix 1-B) which provide information concerning the etiological associations of infantile spasms we identified 200 specific disorders or pathological conditions (Table 9.2) that have been considered to be etiological or predisposing factors by the investigators. These factors include numerous genetic disorders, both inherited and isolated, cerebral neoplasms, toxins, trauma, hypoxia/ischemia, infections, vascular disorders, and many conditions of uncertain, mixed or variable origin. It is important to be aware that the vast majority of these factors have not been proven to be causally associated with infantile spasms. In most cases, the association between a particular factor and the occurrence of infantile spasms is based on one, or a few, case reports or small collected series of patients, and consequently there is the very real possibility that some such associations are simply coincidental, reflecting the fact that both infantile spasms and the condition in question can occur during the same time period. The danger inherent in such coincidental associations is best illustrated by the controversy that has surrounded the relationship between childhood vaccination and infantile spasms. Many investigators included vaccination as an etiological factor in the past, and the consequences had an adverse effect on medical care which is not yet completely resolved (see Section 4, below). While it is now clear that vaccination is not an etiological factor, and that the relationship is purely coincidental, many years of effort, at great expense, were required to clarify the situation. Consequently, with only a few exceptions, the conditions and disorders listed in Table 9.2 should be considered to be potential etiological factors, as yet unproven. In general, establishment of a true causal relationship requires demonstration that the incidence of infantile spasms is higher in groups of subjects exhibiting the potential etiological factor than it is in the general population. Alternatively, a causal relationship is also suggested if it can be demonstrated that the incidence of the potential etiological factor itself is higher among infantile spasms patients than in the general population. In the following discussion of the various individual factors, we have provided, whenever possible, information that supports a true causal relationship and these selected conditions are listed separately in Table 9.3.

3.2 Genetic factors

Table 9.2, section A, lists 91 conditions or syndromes that have been reported to occur in association with infantile spasms, and that are considered to be genetically-based. These entities include both inherited or familial cases and sporadic or isolated occurrences.

Table 9.2

Reported pathological associations and predisposing factors for infantile spasms

(Reference numbers refer to listing in Appendix 1-B)

A. Genetic (proven or probable) (includes familial and isolated cases)

Neurocutaneous syndromes

Tuberous sclerosis (10, 14, 15, 16, 20, 37, 41, 46, 47, 48, 70, 73, 89, 90, 94, 102, 112, 122, 126, 142, 145, 150, 152, 154,159, 168, 176, 177, 178, 181, 185, 192, 193, 195, 197, 200, 201, 203, 210, 212, 213, 214, 220, 229, 243, 247, 251, 255, 256, 268, 269, 285, 286, 288, 290, 292, 293, 296, 300, 305, 306, 317b, 318, 320, 235, 237, 324, 326, 328, 335, 336, 346, 350, 359, 365, 376, 391, 394, 398)

Encephalocraniocutaneous lipomatosis (Fishman syndrome) (9)

Neurofibromatosis (23, 40, 47, 48, 90b, 93, 152b, 179, 185, 193, 212, 236, 247, 293, 328, 356)

Sturge-Weber syndrome (23, 99, 185, 197, 220, 296, 380)

Sjogren-Larsson syndrome (23)

Hypomelanosis of Ito (incontinentia pigmenti achromians) (23, 85, 271, 353)

Nevus linearis sebaceous (of Jadassohn) syndrome (23, 136, 187, 193, 207)

Epidermal nevus syndrome (190, 193, 273, 309)

Organoid nevus syndrome (52)

Neurocutaneous melanosis (208)

Cranioencephalic cutaneous angiofibromatosis (244)

Incontinentia pigmenti (Bloch-Sulzberger syndrome) (25, 48, 96, 185, 193, 197, 314, 327)

Metabolic syndromes

Acyl-CoA-decarboxylase deficiency (296)

Phenylketonuria (10, 14, 16, 89, 90,185, 197, 201, 220, 251, 296, 335, 394, 405)

Cytochrome oxidase deficiency (14, 17, 369)

3-hydroxy-3-methyl-glutaric aciduria (14, 296)

Mitochondrial complex I deficiency (26)

Mitochondrial complex III deficiency (42)

Mitochondrial diabetes (point mutation A3243G) (28, 319b)

Mitochondrial encephalopathy with respiratory chain defects (38)

Leigh syndrome (subacute necrotizing encephalomyelopathy) (25, 38, 165, 197, 237, 296, 347, 369)

Lactic acidemia (48, 181, 225, 247)

Pyruvate dehydrogenase complex deficiency (128, 240, 261)

Proprionic acidemia (48, 306)

Non-ketotic hyperglycinemia/ glycine encephalopathy (69, 197, 206, 247, 293, 296, 364, 383, 403)

Propionyl coenzyme A carboxylase deficiency (ketotic hyperglycinemia) (131, 197)

3-phosphoglycerate dehydrogenase deficiency (134, 278)

Biotinidase deficiency (162)

Maple syrup urine disease (181, 197, 198)

3-methylcrotonylglycinuria (194)

Alper's syndrome (197)

***Table 9.2* (Continued)**

NARP syndrome (mitochondrial DNA point mutation at nt 8993) (202)

Dihydropteridine reductase deficiency (218)

Carnitine palmitoyl transferase II deficiency (253)

Fumaric aciduria (fumarase deficiency) (289)

Carnosinemia (293)

D-Glyceric aciduria (363)

Argininosuccinase deficiency (394)

Globoid cell leucodystrophy (Krabbe's disease) (121, 204)

Menkes disease (48, 319, 351)

Pyridoxine dependency (19, 25, 197, 220, 296)

Tay-sachs disease (335)

Neurodegenerative disorders

Rett syndrome (213, 336, 394)

Wilson's disease (25)

Neuronal ceroid-lipofuscinoses (324)

Disorders associated with malformations, dysplasias, and maldevelopment

Costello syndrome (97)

Fasioscapulohumeral muscular dystrophy (6, 223)

Histidinemia (79)

Hurler's syndrome (mucopolysaccharidosis, gargoylism) (117, 170)

Lowe's oculocerebrorenal syndrome (25)

Marinesco-Sjogren disease (25, 197)

Progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy (PEHO) syndrome (98, 101, 124, 140, 290, 296, 310, 322, 332, 333, 347, 360, 372, 374)

Sudanophilic leukodystrophy (22, 296)

Cornelia de Lange syndrome (185, 197, 290)

PEX6-defective peroxisomal biogenesis disorder (282)

Fahr syndrome (idiopathic basal ganglia calcification) (209)

Schinzel-Giedion syndrome (221)

Kabuki make-up syndrome (222)

DOOR syndrome (284)

Pallister-Killian syndrome (296)

Carbohydrate-deficient glycoprotein syndrome type III (344)

Broad thumbs syndrome (368)

Wiedemann syndrome (392)

Xeroderma pigmentosum group G/ Cockayne syndrome complex (402)

X-linked infantile spasms (33, 51, 86, 272, 308, 317c, 345, 347, 370b)

Aicardi syndrome and related disorders with agenesis of corpus callosum (3, 34, 39, 47, 60, 64male, 72, 75, 109, 125, 127, 138, 145, 177, 181, 185, 197, 198, 213, 217, 225, 246, 247, 251, 254, 290, 293, 296, 330, 335, 340, 352, 355, 365, 376, 393, 394, 396, 397)

CHARGE association (65)

***Table 9.2* (Continued)**

Cerebro-oculo-facial-skeletal (COFS) syndrome (129)

Smith-Lemli-Opitz syndrome (DHCR7 gene mutation on chromosome 11q13) (156, 347)

Angelman syndrome (163, 211, 394)

Chromosomal disorders

Down syndrome (trisomy 21) (10, 20, 40, 48, 84, 94, 101, 112b, 170, 177, 185, 197, 230, 255, 280, 281, 290, 296, 302, 324, 325, 328, 336, 337, 338, 339, 350, 357, 365, 394)

Diploid-triploid mixoploidy (46,XX/69,XXX) syndrome (158)

Proximal inverted duplication of chromosome 15q (24, 36, 296)

Chromosome 18p monosomy (375)

18p syndrome (partial deletion of chromosome 18) (195)

Reciprocal translocation between chromosomes 6q and 14q (132)

Translocation between chromosomes 7 and 12 (177)

15p tetrasomy [47,XY,+ inv dup (15)(pter→q13::q13→pter)] (173)

Partial duplication of chromosome 2p [46,XY, inv dup (2)(p22.1p21)dn] (183, 230)

Williams syndrome (chromosome 7 deletions) (228, 370)

Translocation between chromosomes 12 and 21 (230)

Translocation between chromosomes 1 and Y (230)

Trisomy of chromosome 7q (230, 248)

Duplication of chromosome 18q (230)

Duplication of short arm of X chromosome and unilateral polymicrogyria (270)

Smith-Magenis syndrome (chromosome 17p.11.2 interstitial deletion) (301)

X-autosome translocation with functional disomy for Xq26.3-qter (5)

Chromosome 1p36 deletion syndrome (135)

Wolf-Hirschorn syndrome (chromosome 4p- deletion) (166)

Miscellaneous genetic disorders

Hemophilia A (103)

Vitamin-D-dependent rickets (117)

B. Genetic and / or mixed basis

Neuronal migration disorders/ cerebral cortical dysgenesis

Cortical dysplasia (focal or diffuse) (1, 13, 48, 101, 105, 174, 177, 198b, 226, 312, 336, 356, 376,379, 380, 381, 395)

Band heterotopia (18, 267)

Microgyria (47, 168, 293)

Heterotopia (47, 105, 188, 266)

Polymicrogyria (50, 105, 159, 174, 197, 224, 226, 256b, 266, 336)

Agyria/ pachygyria (lissencephaly) including Miller-Dieker and Walker-Walburg syndromes (27, 47, 76, 105, 106, 123, 130, 141, 159, 160, 167, 168, 174, 177, 210, 213, 224, 225, 227, 234, 237, 247, 276, 293, 296, 304, 313, 336, 342, 404)

Hemimegalencephaly (105, 174, 197, 265, 273, 354, 361)

Bilateral perisylvian syndrome (polymicrogyria) (115, 189)

Schizencephaly (197)

Agenesis of mamillary bodies and olivary-dentate dysplasia (366)

***Table 9.2* (Continued)**

Posterior fossa malformations

Dandy-Walker complex (315, 324)

Arnold-Chiari malformations (315)

Brainstem/cerebellar atrophy (293, 315)

C. Neoplastic

Ganglioglioma (1, 100)

Brainstem medulloepithelioma (7)

Hypothalamic tumor (probable hamartoma) (12)

Cortical oligoastrocytoma (12)

Choroid plexus papilloma (32, 127, 355)

Optic glioma (185)

Hemangioma / cavernous angioma (251)

Glioma (251, 307)

Astrocytoma (251, 285, 287, 317b)

Gangliocytoma (251)

Ependymoma (251, 307)

Embryonal carcinoma (with Aicardi syndrome) (352)

D. Toxic (exogenous)

Toluene embryopathy (11, 350)

L-tryptophan administration (in Down syndrome) (4, 293)

5-hydroxytryptophan administration (in Down syndrome) (53)

Lead toxicity (2, 197)

Lithium toxicity (2, 197)

Theophylline administration (323)

Ketotifen administration (Histamine H1 antagonist) (399, 399b, 400)

E. Traumatic

Abdominal trauma (maternal)

Birth trauma (16, 90, 110, 46, 89, 91, 139, 159, 170, 185, 186, 210, 220, 235, 331)

Head injury (90, 91, 101, 185, 186, 212, 220, 249, 326)

Subdural hematoma (16, 101, 159, 225)

Cardiac surgery with deep hypothermia (83)

Post-neurosurgery (377)

F. Hypoxic - Ischemic

Periventricular leukomalacia (40, 66, 101, 168, 197, 199, 257, 258, 259, 263, 317, 395)

Hypoxic-ischemic encephalopathy (10, 14, 20, 43, 44, 45, 66, 78, 91, 101, 153, 177, 178, 185, 192, 197, 210, 212, 213, 225, 231, 235, 258, 260, 269, 277, 286, 293, 306, 311, 317, 317b, 321, 324, 326, 356, 365, 376, 385, 386, 388, 394)

Cardiorespiratory insufficiency (20, 197, 247, 358, 382, 388)

Near-miss sudden infant death syndrome (54, 376)

Near-drowning (104, 147, 197, 324)

Choking (185)

G. Infectious

Intrauterine infection (14, 20, 139, 197, 212, 247, 288, 358, 365, 382)

***Table 9.2* (Continued)**

Congenital toxoplasmosis (16, 116, 185, 324, 331, 393)

Congenital syphilis (110, 231, 393)

Congenital rubella (250, 393)

Cytomegalovirus (congenital or acquired) (56, 88, 137, 291, 294, 343, 358, 393, 394)

Meningitis (viral and bacterial) (10, 110, 159, 182, 185, 197, 210, 212, 231, 235, 255, 288, 294, 296, 311, 317, 317b, 321, 324, 346, 356, 358, 365, 376, 382, 386, 388, 394)

Encephalitis (viral and bacterial) (16, 108, 110, 180, 182, 185, 197, 210, 212, 220, 235, 252, 287, 288, 294, 317, 317b, 321, 339, 346, 356, 358, 371, 376, 385, 394)

Cysticercosis (95)

Brain abscess (197)

Sepsis (20, 185, 247, 311)

H. Vascular

Intracranial/intraventricular hemorrhage (14, 20, 43, 44, 66, 94, 185, 192, 212, 213, 247, 260, 296, 311, 318, 321, 346, 356, 382, 388)

Middle cerebral artery thrombosis (329)

Intracranial aneurysm (74, 293)

Cerebral infarct (8, 356, 350, 359)

Malformation of vein of Galen (155, 350)

Intracranial hemorrhage (197, 247, 288, 293, 385)

Cerebellar infarct (315)

Arteriovenous malformation (346)

I. Uncertain or mixed basis

Holoprosencephaly (47, 251, 255, 316, 387)

Primary immunodeficiency (IgA;IgM) (35, 185)

Familial infantile spasms without a clear genetic basis (71, 82, 87, 144, 274, 288b, 303)

Fibromatosis of dura/ tentorium cerebelli (77)

Reye syndrome (107, 185, 245)

Congenital hydrocephalus (133, 185)

Malformation of lenticular nucleus (159)

Focal segmented glomerulosclerosis with nephrotic syndrome (161)

Porencephaly (110, 168, 169, 175, 185, 198, 210, 224, 226, 251, 255, 262, 277, 317, 318, 324)

Septo-optic dysplasia (177, 184, 191, 401)

Septum pellucidum cyst (185)

Cavum Vergae (sixth ventricle) cyst (185)

Hydrancephaly (185, 242, 251, 290, 324)

Aplasia cutis congenita (205)

Neonatal hemangiomatosis (215)

Ependymal cyst associated with multiple pineal cysts (264)

Multiple developmental anomalies (279, 293)

Lorber syndrome (293)

Arthrogryposis multiplex congenita (multiple congenital contractures) (328)

***Table 9.2* (Continued)**

Low CSF homovanillic acid level (348)

Soto syndrome (cerebral gigantism) (349)

Encephalomeningocele (293, 328, 356)

Microspongiosis of cerebral cortex (362)

Focal delayed myelination (384)

J. Miscellaneous

Dehydration (14, 78, 170, 376)

Maternal preeclampsia/ toxemia (14, 16, 66, 185, 197, 324)

Maternal uterine bleeding (16, 45, 91, 139, 170, 197, 324)

Birth weight less than expected for gestational period (58, 185, 197, 212, 324)

Fever of unknown origin (89, 90)

Hyperbilirubinemia / kernicterus (89, 90, 110, 185, 331)

Prematurity (10, 89, 90, 139, 181, 185, 195, 210, 212, 331)

Neonatal hypoglycemia (14, 92, 296, 394)

Febrile convulsion, prolonged (101)

Weaning from breast milk containing anticonvulsants (172)

Attempted or threatened abortion (139,185)

Hypoglycemia (20, 185, 197, 224, 225, 293, 324, 335, 358, 359, 388)

C-section (139, 185, 197, 331)

Premature rupture of membranes (185)

Abruptio placentae (185, 197, 336)

General anesthesia (185)

Maternal diabetes (16, 197)

Maternal drug addiction (197)

Hydrocephalus (235, 247, 251, 290, 293, 296, 382)

Microcephaly (237, 251)

Hypothyroidism (306)

Neonatal hypocalcemia (tetany of newborn) (367)

Table 9.3 **Probable etiological or predisposing factors for infantile spasms ***

Condition or disorder	*Percentage of IS patients with the condition* ***
Hypoxic-ischemic encephalopathy (10,14,20,78,91,101,153,177,178,185, 210,213,277,306,311,317,317b,324,356,385,386,388,394)	21.6% (2.9-63.0%)
Tuberous sclerosis (10,14,16,20,46,47,48,90,94,112,122,145,177,178,181, 185,192,195,197,201,210,212,213,220,235,237,247,251,255,256,288,293,296,306, 621c,318,324,326,328,336,346,350,359,365,376,394)	10.7% (1.4-33.3%)
Intracranial/intraventricular hemorrhage (14,20,185,212,213,247,311,	7.2% (1.0-27.7%)
Periventricular leukomalacia (101,317)	6.7% (2.7-10.6%)
Low birth weight for gestational period (58,185,212,324)	6.3% (1.5-12.8%)
Aicardi syndrome** (47,145,177,181,185,213,247,251,290,293,365,376,394)	4.9% (1.9-16.3%)
Down syndrome (10,20,48,101,185,255,290,296,324,328,336,250,365,394)	4.6% (0.7-10.5%)
Phenylketonuria (10,14,16,90,185,201,220,251,394)	2.3% (0.1-8.6%)
PEHO syndrome** (101,290,296)	2.0% (0.4-2.9%)
Lissencephaly (47,210,213,247,293,296)	1.4% (0.4%-4.3%)
Neurofibromatosis type 1 (47,48,90b,185,212,247,293,328,356)	1.4% (0.4-3.6%)
Angelman syndrome (394)	1.0%
Pyruvate dehydrogenase complex deficiency	(not reported) ‡
Hemimegalencephaly	(not reported) ‡
Ito's hypomelanosis	(not reported) ‡
X-linked infantile spasms**	(not reported) ‡
Focal cortical dysplasia	(not reported) ‡

* Reference numbers in parentheses refer to listing in Appendix 1-B, and include only studies reporting the number of infantile spasms cases associated with the condition.

** These disorders include infantile spasms/hypsarrhythmia as an essential component of the syndrome.

*** Average value (not corrected for variable number of patients) and range observed in referenced studies.

‡ Not reported in unselected populations

Neurocutaneous syndromes The neurocutaneous syndromes include a group of congenital entities characterized by dysplastic features involving both the skin and the nervous system. Infantile spasms has been reported to occur in association with 12 of these conditions (Table 9.2, section A), and evidence supportive of a true causal relationship is available for three of these disorders: tuberous sclerosis, neurofibromatosis, and Ito's hypomelanosis.

Tuberous sclerosis is an autosomal dominant disorder with a prevalence of approximately 1/10,000 births, which is characterized by the presence of hamartomas (tubers), which may involve multiple organs, including the central nervous system (Curatolo, 1994; Curatolo et al., 2001). This disorder is associated with variable neurological manifestations, and seizures are common. As indicated in Table 9.2, many investigators have noted an apparent etiological relationship between tuberous sclerosis and infantile spasms, and several of these studies have provided evidence indicating a causal basis. In 15 investigations conducted between 1964 and 1998, the incidence of infantile spasms was evaluated in groups of patients diagnosed as having tuberous sclerosis (della Rovere et al., 1964; Nevin and Pearce, 1968; Fois et al., 1973; Pampiglione and Moynahan, 1976; Mattyus et al., 1977; Debard et al., 1979; Konishi et al., 1979; Maki et al., 1979; Hunt and Dennis, 1987; Yamamoto et al., 1987; Calderon Gonzalez et al., 1994; Shepherd et al., 1995; Ohtsuka et al., 1998; Hamano et al., 1999; Hosoya et al., 1999). In these 15 studies, with group sizes of 11 to 90 patients each, infantile spasms occurred at some time in from 19 to 77% of the cases, with an average value of 55%. Since the incidence of infantile spasms in the general population is approximately 1 case per 3,225 live births (see Chapter 3), which is equivalent to 0.03%, the markedly increased incidence in tuberous sclerosis patients strongly supports a causal relationship. In a number of other studies (see Table 9.3), the incidence of tuberous sclerosis was reported in series of patients diagnosed with infantile spasms. The average value (uncorrected for variable study size) for these investigations (with group sizes of 7 to 757 patients each) was 11% (range 1-33%). In the two largest series (Kurokawa et al., 1980, with 757 cases, and Lombroso, 1983, with 286 cases) the incidence of tuberous sclerosis was 6.1% and 6.6%, respectively. Thus, the frequency of tuberous sclerosis among infantile spasms patients is much higher than its occurrence in the general population (approximately 0.01%, or 1/10,000 births). Consequently, there is considerable epidemiological evidence suggesting that tuberous sclerosis is a predisposing factor for infantile spasms. A positive correlation between the total number of cortical tubers (as detected by MRI) and the development of infantile spasms in patients with tuberous sclerosis has been reported (Shepherd et al., 1995; Hamano et al., 1999), although in a few cases, patients with infantile spasms had only one detectable tuber. While Hamano et al. (1999) also observed that tubers involving the occipital lobes occurred more frequently in patients developing infantile spasms than in subjects who did not develop spasms, Shepherd et al. (1995) did not find a statistically significant relationship with anatomical region.

Neurofibromatosis type 1 is an autosomal dominant genetic disorder with a prevalence in the general population of approximately 1 per 5000, and is associated with multiple café-au-lait spots and/or cutaneous neurofibromas (Huson et al., 1988). In two population-based studies of patients with neurofibromatosis type I, reported by Huson et al. (1988), with 135 cases, and Korf et al. (1993), with 359 cases, the rate of associated infantile spasms was 1.5% and 0.3%, respectively, values which are considerably higher than the 0.03% value for infantile spasms in the general population. In addition, the incidence of neurofibromatosis was 0.4-3.6% (average value 1.4%) in several series of patients (with 28-757 subjects each) diagnosed with infantile spasms (Table 9.3), a value exceeding the reported prevalence of 0.02% (1/5000) for neurofibromatosis in the general population. Consequently, the available evidence is consistent with a causal relationship between neurofibromatosis and infantile spasms.

Hypomelanosis of Ito (incontinentia pigmenti achromians) is a neurocutaneous disorder characterized by hypopigmented skin areas with a typical swirled pattern, and is typically associated with multiple malformations which often involve the nervous system. Neurological complications, including mental retardation and seizures are common. While relatively few cases occurring in association with infantile spasms have been published (Fan et al., 1994; Tagawa et al., 1994a,b), infantile spasms was diagnosed in 8% of the 76 patients with hypomelanosis of Ito studied by Pascual-Castroviejo et al. (1998). This incidence is also considerably higher than the general population value of approximately 0.03% for infantile spasms, and so these findings support a causal relationship for hypomelanosis of Ito. The incidence of this condition among infantile spasms patients has not been reported.

Insufficient information exists regarding the other neurocutaneous syndromes to establish the presence of a causal relationship, although, as indicated in Table 9.2, a number studies have documented an association with infantile spasms.

Metabolic syndromes Table 9.2, section A, lists 29 genetically-based metabolic disorders which have been reported to occur in association with infantile spasms. These disorders are associated with altered function of diverse biochemical pathways, and can be accompanied by a variety of neurological deficits. While several of these disorders have been associated with infantile spasms in multiple case reports or small series, evidence demonstrating a causal relationship is currently available for only two of these conditions: phenylketonuria and pyruvate dehydrogenase complex deficiency.

Phenylketonuria encompasses a complex of gene mutations affecting phenylalanine metabolism, and is inherited in an autosomal recessive manner. The incidence is reported to be approximately 0.01% (1:10,000 to 1:20,000 live births) (Handler et al., 1995). If untreated this disorder is typically associated with mental retardation and other neurological abnormalities, including seizures. In a retrospective analysis of 503 cases of phenylketonuria, Zhongshu et al. (2001) identified 62 patients (12%) who had infantile spasms, an incidence

greatly exceeding the general population value of approximately 0.03% for infantile spasms. The MRI findings in these patients showed evidence for delayed myelination in the cerebral hemispheres and corpus callosum, which was more pronounced that that observed in the patients without infantile spasms. In several series of infantile spasms patients (Table 9.3), with group sizes of 26-757 patients, the incidence of phenylketonuria was found to range from 0.1% to 8.6% (average 2.3%), with all values considerably above the expected general population value of 0.01% for phenylketonuria. Thus, there is consistent evidence supporting a causal relationship between this disorder and infantile spasms.

Pyruvate dehydrogenase complex deficiency is associated with congenital lactic acidemia, and is a result of mutations in the pyruvate dehydrogenase (E1) α subunit gene (Naito et al., 2001). This X-linked recessive disorder is manifested by multiple brain anomalies as well as degenerative changes, and seizures are common (Maertens and Dyken, 1995). Naito et al. (2001) studied 60 patients diagnosed with this disorder (30 males and 30 females) and found 10 cases with infantile spasms (17%). Nine of these 10 patients were female, resulting in an incidence of 30% for females, as compared to 3% for males. Both of these values are well above the expected infantile spasms incidence value of 0.03% for the general population, suggesting that pyruvate dehydrogenase complex deficiency is a true etiologic factor for infantile spasms. There have, however, been few case reports of this association (Otero et al., 1995; Harada et al., 1996).

While numerous case reports have documented the association of infantile spasms and many other genetic metabolic syndromes, as indicated in Table 9.2, section A, insufficient information regarding the relative incidence of these conditions exists to permit a causal relationship to be more firmly established. The possibility that these conditions may be under-reported has been suggested by Shah et al. (2002), who found evidence for defective energy metabolism in 13 of 17 (76%) patients previously classified as cryptogenic (two were determined to have the A3243G mitochondrial mutation).

Neurodegenerative disorders Several neurodegenerative disorders have been associated with infantile spasms in published case reports (Table 9.2, section A) including Rett syndrome, Wilson's disease, and neuronal ceroid-lipofuscinoses. However, there have been no published studies of these disorders that provide definitive information regarding causal relationships to infantile spasms. (Note: several other genetic disorders often considered to be neurodegenerative in character have been included in Table 9.2 within other categories.)

Disorders associated with malformations, dysplasias and maldevelopment This category includes 26 genetically-based conditions that are associated with a variety of neuropathological processes, and which have been associated with infantile spasms (Table 9.2, section A). However, a causal relationship has been established for only four of these disorders: progressive encephalopathy with

edema, hypsarrhythmia, and optic atrophy (PEHO) syndrome, Aicardi syndrome, Angelman syndrome, and X-linked infantile spasms.

The *progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy (PEHO) syndrome* is characterized by the onset of progressive encephalopathy in early infancy, edema of the extremities and face, infantile spasms with hypsarrhythmia, and central nervous system atrophy, involving primarily the optic nerve, cerebellum, and brainstem (Salonen et al., 1991; Haltia and Somer, 1993; Somer, 1993; Tanaka et al., 1997). However, minimally disturbed cytoarchitecture of the cerebral cortex is also reported (Haltia and Somer, 1993). The disorder is typically familial, and is transmitted in an autosomal recessive mode. The syndrome was described initially by Salonen et al. (1991), and has been confirmed in a number of subsequent studies (Table 9.2, section A). The genetic basis of this disorder is still unknown, as are the basic pathological mechanisms, and thus it is unclear at this time whether or not this disorder is a distinct syndrome with a unique basis. Recent findings by Vanhatalo and Riikonen (2000) have suggested that production of nitric oxide is markedly increased in this disorder (as measured in the CSF), and could be a factor underlying the degenerative process. Since the presence of infantile spasms and hypsarrhythmia is an integral component of the syndrome, an etiological relationship is necessarily established. In three studies (Table 9.3) that have reported the frequency of occurrence of this syndrome in series of infantile patients, with group sizes of 38 to 448 patients, the average incidence was 2.0% (range 0.4-2.9%).

The *X-linked infantile spasms syndrome* was described initially by Feinberg and Leahy (1977), who studied 5 male children in three successive generations of a single family who developed infantile spasms. The pedigree was consistent with an X-linked recessive mode of inheritance, and, other than mental retardation, the children did not have characteristics suggestive of any other specific disorder. Since then a number of additional reports describing similar familial associations have been published (Table 9.2, section A). More recently, specific loci on the X chromosome have been identified in association with this disorder through the use of linkage analysis including Xpter-Xp11.4 (Claes et al., 1997), Xp21.3-Xp22.1 (Bruyere et al., 1999), Xp11.4-Xp22.11 (Stromme et al., 1999) and Xp11.2-22.2 [ARX gene mutation] (Stromme et al., 2002; Scheffer et al., 2002; Turner et al., 2002).

Aicardi syndrome is characterized by agenesis of the corpus callosum, ocular abnormalities (chorioretinal lacunae), and infantile spasms (Aicardi et al., 1969). In addition, cortical migration defects have been found to be present (by MRI evaluation) in most patients (Smith et al., 1996). These patients are often mentally retarded, and may have other developmental anomalies, such as cortical heterotopias and cerebellar hypoplasia (Hamano et al., 1989). This disorder typically occurs sporadically (i.e., new mutations), and is considered to be an X-linked dominant condition resulting from a balanced translocation involving the X chromosome. The condition is found almost exclusively in females,

suggesting that the abnormality is usually lethal in males. Numerous case reports and series have been published since the original description, and have confirmed the essential elements of the syndrome (Table 9.2, section A). Aicardi syndrome includes infantile spasms as an essential feature of the disorder, and so a causal relationship is presumed to be present. The incidence of this condition in several series (with group sizes of 28-230 subjects) of infantile spasms patients (Table 9.3) has ranged from 1.9-16.3% (average value 4.9%).

Angelman syndrome (happy puppet syndrome) is characterized by dysmorphic features, puppet-like posture with an ataxic gait, inappropriate laughter, mental retardation, and seizures. This genetic disorder occurs sporadically, and is due to an interstitial deletion involving the maternal chromosome 15q. While very few case reports have been published documenting an association with infantile spasms (Kalmanchey and Halasz, 1990; Wong, 2001), in a study of 8 patients with Angelman syndrome, Matsumoto et al. (1992) found that 3 (38%) had infantile spasms. Since this represents an incidence of infantile spasms much higher than the general population value of approximately 0.03%, the findings suggest a causal relationship.

Most of the other 22 disorders in this category have been associated with infantile spasms only rarely, and inadequate data exist to establish a causal relationship.

Chromosomal disorders This category includes 19 disorders resulting from known chromosomal anomalies, including duplications, deletions, inversions, and translocations (Table 9.2, section A). While all have been reported in patients with infantile spasms, only one, Down syndrome, has been studied sufficiently to establish a definite causal relationship.

Down syndrome (trisomy 21) is a relatively common disorder, occurring in approximately 1 per 1000 live births, and is manifested primarily by characteristic dysmorphic features, mental retardation, increased incidence of congenital cardiac and gastrointestinal abnormalities, hypotonia, and an increased probability of seizures. The most common genetic abnormality is trisomy 21, although other chromosome 21 defects are occasionally responsible (Berg, 1999). In several studies which investigated the occurrence of seizure disorders in Down syndrome (group sizes 113-844 patients each), the incidence of infantile spasms ranged from 0.8% to 3.5% (average value 2.1%), values greatly exceeding the expected incidence of 0.03% for infantile spasms in the general population (Tatsuno et al., 1984; Romano et al., 1990; Pueschel et al., 1991; Stafstrom et al., 1991; Escofet et al., 1995; Goldberg-Stern et al., 2001). Similarly, the relative incidence of Down syndrome in groups of patients with infantile spasms is higher than the expected value of 0.1% in the general population. In the 14 studies listed in Table 9.3, with group sizes of 11 to 757 patients, the average percentage of infantile spasms patients with Down syndrome was 4.6% (range 0.7% to 10.5%). These findings clearly demonstrate a causal relationship between Down syndrome and infantile spasms.

Miscellaneous genetic disorders Hemophilia A was reported in a single case with concurrent infantile spasms (Ganesan and Kirkham, 1996), and vitamin D-dependent rickets was documented in another isolated case, also associated with Hurler's syndrome (Guidino et al., 2002). The rarity of such associations suggests a coincidental relationship.

3.3 Factors with a genetic and/or mixed basis

The conditions included in Table 9.2, section B, (neuronal migration disorders, cerebral cortical dysgenesis, and certain posterior fossa malformations) have been listed separately from the preceding group of genetic disorders since the pathophysiological basis is considered to be mixed. While the basis is clearly genetic in some instances, other mechanisms, including environmental factors and trauma, can also be involved.

Neuronal migration disorders/ cerebral cortical dysgenesis The 10 conditions included in this category that have been reported to occur in association with infantile spasms result from faulty neuronogenesis, which can result in a wide variety of cerebral malformations. Sufficient evidence is available to suggest that two of these disorders, lissencephaly (agyria/ pachygyria) and hemimegalencephaly, can be considered to be causal or predisposing factors with respect to infantile spasms. Cortical dysplasia is also a probable causal factor, although currently available evidence is considered to be inconclusive.

Agyria/pachygyria (lissencephaly). Lissencephaly (smooth brain) is characterized by an absence of cerebral convolutions, while pachygyria is associated with rare, broad gyri and shallow sulci (Encha-Razavi, 1995). While some cases have a clear genetic basis, a variety of pathological factors appear to be capable of producing this condition. As indicated in Table 9.2, section B, this condition has frequently been reported to occur in association with infantile spasms. While many investigations have not provided quantitative information regarding the frequency of this condition in infantile spasms, in the 6 studies referenced in Table 9.3 (with group sizes of 47-256 patients), the average frequency of lissencephaly was 1.4% (range 0.4% to 4.3%). In addition, a very high incidence of infantile spasms has been reported in several small series of patients with lissencephaly. Hakamada et al. (1979) studied 3 cases of lissencephaly, all of whom developed infantile spasms, and similar findings were reported by Pavone et al. (1993), with all 7 of their patients exhibiting infantile spasms. Mori et al. (1994) followed 12 cases of lissencephaly with serial studies, and found that 5 developed infantile spasms (42%). Thus, this condition appears to be a causal factor in infantile spasms.

Hemimegalencephaly is a congenital malformation associated with hypertrophy of one cerebral hemisphere, with ventricular enlargement and displacement of midline structures (Paladin et al., 1989). Several studies have reported an association of this condition with infantile spasms (Table 9.2, section

B). In a study of 12 patients with hemimegalencephaly, Paladin et al. (1989) reported that 3 had infantile spasms (25%). Pavone et al. (1991) evaluated 60 patients with the epidermal nevus syndrome, and determined that 17 of these subjects had hemimegalencephaly, and that 9 of these (53%) also had infantile spasms. Consequently, there is substantial evidence suggesting an etiological role for this condition.

Cortical dysplasia (focal or diffuse) is a disorder of neuronal migration resulting in structural abnormalities of the cerebral cortex and subcortical white matter which include disordered lamination, neuronal dysmorphism, blurring of the cortex-white matter junction, and other atypical features (Vinters et al., 1999). This condition has been noted in association with infantile spasms in a number of studies (Table 9.2, section B). According to Vinters (2002) cortical dysplasia is the most common neuropathologic abnormality found in cortical resections conducted for the treatment of infantile spasms. Such lesions may not be detected clinically, or by CT and/or MRI imaging techniques, but often correspond to areas of focal or diffuse metabolic dysfunction, as revealed by positron emission tomography (Chugani and Conti, 1996). In a retrospective study of 28 patients with focal cortical dysplasia, identified by neuroradiological features or histological findings (following cortical resections), Lortie et al (2002) found that 11 (39%) developed infantile spasms. Because of the highly selected character of the patient population (all had seizures) and the likelihood that referral patterns influenced the proportion of patients with infantile spasms, this value can not be assumed to be representative of cortical dysplasia in general. But, considering all of the available evidence, it does seem likely that cortical dysplasia is a causal factor for infantile spasms.

Posterior fossa malformations Several case reports have been published reporting the occurrence of infantile spasms in association with the Dandy-Walker complex, Arnold-Chiari malformations, and brainstem/cerebellar atrophy (Table 9.2, section B). There is, however, insufficient information to demonstrate a definite causal relationship in any of these disorders.

3.4 Neoplastic disorders

As indicated in Table 9.2, section C, a number of reports have documented an association between infantile spasms and the presence of intracranial neoplasms of several types. However, there have been no studies demonstrating an increased occurrence of infantile spasms in such disorders beyond that expected in the general population. Consequently a true etiological role for these neoplasms in the production of infantile spasms remains uncertain.

3.5 Toxic factors

The occurrence of infantile spasms following exposure to toxic, or potentially toxic, agents, either in utero or postnatally, has been reported in several

publications (Table 9.2, section D). While at least some of these agents would be expected to produce neurological damage, and thus can be considered potential etiological factors, no studies have documented the presence of an increased incidence of infantile spasms in unselected patients with similar exposures.

3.6 Trauma

Pre-, peri-, and post-natal trauma has been implicated as a potential etiological factor in infantile spasms in a number of publications (Table 9.2, section E). There is, however, no direct evidence to indicate that any of these entities are associated with an increased incidence of infantile spasms, as opposed to a coincidental relationship. On the other hand, since birth trauma and postnatal head injury are important causes of intracranial hemorrhage, itself a proven etiological factor (see section 3.9, below), these entities can at least be considered to be indirect causal agents. Additional studies are needed to more clearly determine the possibility of other etiological mechanisms associated with head trauma.

3.7 Hypoxic-ischemic factors

Neurological injury resulting from hypoxia and/or ischemia has long been recognized as a likely etiological factor in infantile spasms. As indicated in Table 9.2, section F, there have been many publications documenting this association with respect to 6 specific entities associated with hypoxia/ischemia. At the present time, the available evidence supports a causal relationship with infantile spasms for two of these entities: periventricular leukomalacia and hypoxic-ischemic encephalopathy.

Periventricular leukomalacia is characterized by multiple lesions in the white matter lateral to the ventricles which are a result of hypoxic-ischemic injury, and is relatively specific for preterm infants (Okumura et al., 1996). In some cases, atrophy and other abnormalities are present in other brain areas as well. This condition has been identified as a possible etiological factor in many cases of infantile spasms (Table 9.2, section F). Two investigations have also documented a significantly increased occurrence of infantile spasms in groups of preterm patients diagnosed with periventricular leukomalacia. Okumura et al. (1996) found infantile spasms to be present in 7 of 27 patients (26%) with this condition, and Okumura and Watanabe (2001) reported similar results, with 7 of 22 patients (32%) developing infantile spasms. These findings strongly support a causal or predisposing relationship. In two studies that reported the incidence of periventricular leukomalacia in patients with infantile spasms (Table 9.3), the average value was 6.7% (range 2.7-10.6%). Ozawa et al. (1998) observed that their patients with periventricular leukomalacia who also developed infantile

spasms had concurrent midbrain and pontine atrophy, whereas those who did not develop infantile spasms had no evidence of such atrophy.

Hypoxic-ischemic encephalopathy refers to a wide spectrum of brain injury resulting from presumed episodes of anoxia and ischemia in the perinatal period, and is typically applied to the term infant. As indicated in Table 9.2, section F, a very large number of published studies have found an association between hypoxic-ischemic encephalopathy and infantile spasms. But, in spite of the relatively high frequency of occurrence of this condition, there have been no large studies in which the incidence of infantile spasms was determined. However, in two small series of patients with hypoxic-ischemic encephalopathy infantile spasms was frequent, occurring in 5 of 7 patients (71%) reported by Okumura and Watanabe (2001), and in 6 of 9 patients (67%) studied by Otani et al. (1990). In addition, a high percentage of patients with infantile spasms are reported to have had hypoxic-ischemic encephalopathy. In the 25 studies referenced in Table 9.3, which involved populations ranging from 12 to 757 patients, the average value was 21.6%, with a range of 2.8% to 62.9% observed in the individual series. These finding suggest that this condition is likely to be a true etiological or predisposing factor for infantile spasms.

3.8 Infections

Table 9.2, section G, lists 11 specific infectious disorders that have been associated with the development of infantile spasms, including in utero or congenital processes, as well as postnatal infections. While several of these conditions, in particular, various types of meningitis and encephalitis, have been reported as etiological factors in a large number of studies, there have apparently been no studies in which the relative incidence of infantile spasms was determined within groups of patients diagnosed with these specific conditions. Consequently, while a causal role seems likely in some of these conditions, the currently available data is insufficient to establish the relationship.

3.9 Vascular factors

Section H, Table 9.2 lists 8 vascular factors which have been associated with infantile spasms in a number of studies. Adequate information to establish a causal relationship with infantile spasms is not available for any of these entities, although some evidence supports a role for intracranial/ intraventricular hemorrhage.

Intracranial/intraventricular hemorrhage typically occurs in the perinatal period, and is particularly frequent in premature infants. This condition apparently is multifactorial in origin, with changes of cerebral blood flow, hypoxia, and other factors being involved (Vinters, 1995). Intracranial/intraventricular hemorrhage has been implicated as an etiological factor in a number of published studies of infantile spasms patients (Table 9.2,

section H). In one very large series, Kurokawa et al. (1980) listed intracranial hemorrhage as the likely etiological factor in 13 of 757 cases (1.7%). In a number of smaller studies (Table 9.3) of infantile spasms patients, intracranial/intraventricular hemorrhage was observed in 1.0 to 27.7% of the cases. In a small study of 7 preterm infants with intraventricular hemorrhage, Otani et al. (1990) reported that 4 patients (57%) developed infantile spasms. These findings suggest a causal relationship, but additional epidemiological evidence is needed. Also, this condition may be closely correlated with periventricular leukomalacia, since both often occur in the same patient.

3.10 Factors with an uncertain or mixed basis

A number of entities are listed in section I, Table 9.2, which have an uncertain basis, or which can result from multiple underlying factors. These 24 conditions have been associated with infantile spasms in one or more studies, although insufficient evidence has accumulated to establish any as a definite causal factor. Several, including holoprosencephaly, porencephaly, and hydrancephaly have been identified as potential etiological factors in a number of studies.

3.11 Miscellaneous factors

The last section (J) of Table 9.2 list 22 miscellaneous conditions that have been associated with infantile spasms in published studies. While several of these entities have been reported as etiological factors in multiple studies, only one, low birth weight, has sufficient supporting evidence to suggest a true causal relationship.

A *birth weight less than expected for gestational age* (small-for-dates), as well as prematurity, have been identified as possible etiological factors in a number of studies (Table 9.2, section J). Several studies (with group sizes of 50-757 patients) have reported the number of infantile spasms patients who had birth weights lower than expected for the gestational period (Table 9.3), with an average value of 6.3% (range 1.5-12.8%). This factor was studied in detail by Crichton (1968) who found 38 low birth weight infants (<2,500 g) among 242 cases of infantile spasms (16%). Of these 38 cases, 31 (82%) were small-for-dates, while only 7 (18%) were true prematures. In this study, the small-for–dates infants accounted for 12.4% of the infantile spasms group (38/242), while the incidence of small-for-dates infants in the general population was determined to be only 2.8%. Consequently, this factor appears to be causally related to infantile spasms, although it is not clear to what extent this relationship may simply reflect the presence of other underlying conditions (e.g., intraventricular hemorrhage and periventricular leukomalacia) in the small-for-dates children which could predispose to both infantile spasms and growth retardation.

4. RELATIONSHIP TO CHILDHOOD VACCINATION

4.1 History and early reports

A major controversy has existed over the past 50 years regarding the possibility that childhood vaccination could be an etiological factor responsible for some cases of encephalopathy, including infantile spasms. While sporadic reports dating back nearly 70 years (e.g., Madsen, 1933) have documented neurological disorders occurring immediately following vaccination against pertussis, the most influential report was probably that of Byers and Moll (1948). These investigators, prompted by earlier reports, as well as by their own observations, searched hospital records for the prior 10 year period for cases in which a serious neurological disorder began within 72 hours of pertussis immunization. They located 15 cases, which were described in detail, in children 5 to 18 months of age. It is not clear whether or not any of these children had infantile spasms, although all had seizures. This study, which has often been cited as evidence supporting a causal relationship between pertussis vaccination and childhood encephalopathy, had significant shortcomings, and did not, in fact, provide any proof of an etiological relationship. First, no information was provided concerning the total number of records searched to acquire the 15 cases described, nor was any analysis made with respect to similar cases which may have occurred in children of the same age at other times (such as in the 72 hours preceding pertussis immunization). Instead, the investigators controlled for the possibility of coincidence by searching the same hospital records for encephalopathy following smallpox vaccination. Because only 8 such cases were found, in spite of the fact that more children had been immunized against smallpox, they concluded that the risk was significantly higher for pertussis vaccination. However, this was not an adequate control since the smallpox vaccine was given to school age children, while the pertussis vaccine was received by infants, an age group much more likely to develop encephalopathy. Consequently, this influential study did not provide substantial evidence in support of a cause and effect relationship and the probability that the results were due to coincidence was not ruled out.

In a somewhat similar study that focused specifically on infantile spasms, Baird and Borofsky (1957) identified 51 cases through a retrospective review of EEG records, and determined that of 24 cases with normal development prior to onset of spasms, 9 followed DPT immunization by 2-15 days, whereas only 4 of the 24 children who developed infantile spasms had not been immunized. Although, again, there was no analysis of the distribution of all cases with respect to immunization history, and in spite of the small number of cases, they concluded that "The evidence that DPT immunization may be a factor in the production of infantile myoclonic seizures is suggestive but not clear-cut". They based their conclusion primarily on the fact that the onset "... followed DPT immunization so closely that a cause and effect relationship would have to be

considered." Following the same line of reasoning, Bower and Jeavons (1960) found that of 21 cryptogenic cases of infantile spasms, 11 had onset of spasms within 7 days of immunization (DT, smallpox, or polio), and concluded that "...we have become increasingly convinced that the brain damage is at times due to immunization (not always against pertussis)." While recognizing the possibility of a coincidental relationship, they state that "It is easy to dismiss such an association as coincidence, particularly since a large number of infants are being immunized at this age and this clinical entity is rare. However, in each case the history is impressive." Subsequent case reports have added additional "evidence" interpreted as supporting the above view (e.g., Kringelbach and Senstius, 1966; Kulenkampff et al., 1974; Cavanagh et al., 1981).

4.2 Legal and social ramifications

Reports such as those reviewed above were widely discussed among practicing physicians and parents of patients, with the result that during the 1970s and 1980s, there was an increasing tendency to attribute cases of childhood encephalopathy, including infantile spasms, to vaccination, and this, in turn fostered an increasing number of lawsuits directed against physicians who performed the immunizations and manufacturers who supplied the vaccines. Physicians themselves often contributed to this phenomenon by offering testimony supporting a causal role of the vaccine in order to help parents obtain compensation for these devastating disorders. It has been estimated that in 1986 alone there were 255 lawsuits filed against manufacturers, with an average amount sought of $16.7 million per case (Hinman, 1988). One result of these developments was the passage of the National Childhood Vaccine Injury act in the United States, with implementation in 1988. This program provides for no-fault awards to "injured children" when it can be proven that the onset of encephalopathy began within a specific time period following an immunization (Goldman, 1988). Similar programs were instituted in other countries as well. While such programs have been applauded by many, since they provide much needed resources to families of children with this disorder, they, unfortunately, funnel all such tax-derived funds to a minority of families, chosen, as is now clear, by factors based solely on a coincidental occurrence, while excluding the majority of families affected by this disorder.

Another adverse consequence of this situation was a decline in the use of pertussis immunization in several countries due to fear of the reported neurological side effects. For example, after the deaths of two children in Japan were attributed to pertussis immunization, the vaccine was withdrawn from use in that country. As a result, in the next few years more than 35,000 children contracted whooping cough, with 118 fatalities reported (Fulginiti, 1984). Similarly, as a result of decreased immunization in England, an epidemic of pertussis involving more than 65,000 cases occurred, with 14 deaths reported

(Fulginiti, 1984). Thus, the morbidity associated with the disease far exceeded the number of cases attributed to vaccine injury.

4.3 Evidence against immunization as a causal factor

The shortcomings of the studies reviewed above (section 4.1) were apparent to many investigators from the outset, who were convinced that the findings suggesting an etiological relationship between childhood vaccination and infantile spasms (as well as other encephalopathies) could be adequately explained by simple coincidence due to the fact that early childhood encephalopathies occurred most frequently (whether a child was immunized or not) during the same time period that vaccination was typically performed. As early as 1971, Melchior (1971) wrote "A survey of the literature gives no proof for other connection between immunization (particularly whooping cough) and infantile spasms but a time relation." Griffith (1974) came to the same conclusion, and made the additional interesting point that, for similar reasons, childhood convulsions were in the past attributed to teething, which occurred around the same time that seizures typically were manifested. A number of other investigators made similar conclusions, based upon review of the available reports (e.g., Prensky, 1974; Fukuyama et al., 1977; Fenichel, 1982).

More definitive proof of the coincidental nature of the vaccine-encephalopathy relationship began to appear in the late 1970s, and a number of studies since then have solidified this conclusion. Melchior (1977) made a careful analysis of the age of onset of infantile spasms in Denmark, comparing the peak onset times in 113 cases diagnosed between 1970-1975 with those of 86 cases identified from 1957-1967. He found no significant difference between the two series, although vaccinations in Denmark were given at very different ages during the two time periods, thus arguing against a causal relationship. In a prospective study conducted between 1978-1979 in the United States, Cody et al. (1981) evaluated reactions following 15,752 DPT immunizations given to children up to 6 years of age. Serious reactions (convulsions, hypotonic/hyporesponsive episodes) occurred in 18 instances, but no children developed encephalopathy or permanent brain damage. A follow-up study of 16 of these children after 6-7 years confirmed that none had serious neurological damage as a result of the prior episodes (Baraff et al., 1988). There have been several additional studies of childhood immunization (Pollock and Morris, 1983; Hirtz et al., 1983; Walker et al., 1988), and none have provided evidence to suggest an etiological relationship with infantile spasms.

The National Childhood Encephalopathy Study, conducted in England, Scotland, and Wales between 1976 and 1979, was the most extensive and definitive examination of the relationship between infantile spasms and pertussis immunization (Bellman 1983; Bellman et al., 1983; Goodman et al., 1998). This case-controlled epidemiological study identified 269 cases of infantile spasms (among 1,182 cases of serious neurological illness) in the entire study population

(1 case per 7800 live births) during the study period. It was found that 91% of the cases had not received DPT within 28 days of onset, compared to 87% of the control cases. Analysis revealed that there was no significant association between infantile spasms and pertussis immunization in the 28 days before onset. One interesting finding was a slight excess of infantile spasms cases during the 7 days after vaccination, followed by a compensatory deficit of cases in the subsequent 3 weeks. These findings were not statistically significant, but suggested the possibility that vaccination may have triggered an earlier onset of spasms in children who were beginning to develop the disorder, or (as seems more likely) that spasms were detected earlier by heightened vigilance of parents following the immunization procedure. A similar population-based case-control study conducted in the United States (Gale et al, 1994) identified 424 cases of neurological illness, including 10 cases of infantile spasms, within a population of approximately 218,000 children in the 1-24 month age group. This study found no statistically significant increased risk for serious neurological illness in the 7 day period following DTP vaccination.

In the past decade, this extensive evidence against a causal relationship between immunization and infantile spasms (as well as other serious neurological disorders) has convinced most physicians, and a number of task forces and committees convened by medical societies have issued statements confirming this view (e.g., Ad Hoc Committee, 1991; Howson and Fineberg, 1992; Report, 1992; Stratton, et al., 1994). However, while the scientific evidence against such a causal relationship now appears to be overwhelming, this has not ended the debate, with many parents and lay groups, as well as some physicians, continuing to believe that vaccination, especially against pertussis, can be responsible for severe and permanent neurological damage. While no population-based study can ever prove conclusively, and beyond any shadow of doubt, that vaccination never causes neurological damage, such studies can, and have, proven conclusively that the risk of not being immunized against childhood illnesses greatly exceeds any conceivable risk associated with receiving the vaccine.

5. DISCUSSION AND SYNTHESIS

Of the 200 potential etiological factors identified in our review of more than 400 publications providing information regarding the apparent causes of infantile spasms, only 16 are supported by studies that demonstrate or suggest that the relationship can not be explained by chance or coincidence. These 16 entities, listed in Table 9.3, are not necessarily the most common causes of this disorder, but are simply the categories for which the best information is currently available. Exclusion of a potential etiological factor from this listing should also not be interpreted as indicating that the particular disorder is <u>not</u> causally related to infantile spasms. As we have discussed above, in most cases the necessary comparative and epidemiological studies have simply not been done. In some

instances, this reflects the fact that the factor itself is very rare, and thus it would be difficult to acquire enough cases for a meaningful analysis. In other cases, however, such studies are certainly feasible.

In spite of these limitations to our knowledge of the etiological basis of this disorder, the classification of a patient with infantile spasms into the cryptogenic category – indicating an apparent absence of evident etiological factors and normal development until the time of onset – has proven to be of practical value in clinical management. Cryptogenic patients are more likely to respond favorably to treatment (see Chapter 11) and to have a favorable outcome with respect to both mental development and long-term seizure control (see Chapter 12).

6. FUTURE RESEARCH

Much more definitive information is needed regarding the significance of the large number of potential etiological factors that have been identified in association with infantile spasms. The above review demonstrates how few of these factors have been properly investigated, and that in only a handful of instances can it be concluded that a true causal relationship has been established. It is likely that many of the factors listed in Table 9.2 actually do have such a relationship, and would be demonstrated in carefully designed studies. As we have mentioned previously, every attempt should be made to demonstrate that unselected groups of patients who exhibit specific disorders that have been observed in association with infantile spasms actually have an increased incidence of infantile spasms, as compared to the incidence in the general population. Additional evidence favoring an etiological relationship can be provided by demonstrating that groups of patients with infantile spasms are more likely to exhibit the factor in question than are normal, or other disease, control subjects.

While it may prove to be true, as many have suspected, that essentially any factor that produces brain injury at a particular phase of nervous system development can trigger infantile spasms, the limited data currently available suggest that some factors do so more readily than others. For example, the very high incidence of infantile spasms in tuberous sclerosis, as compared to certain other conditions, including other neurocutaneous syndromes, strongly suggests that there is something unique about the pathophysiological process in tuberous sclerosis which makes it significantly more likely to initiate the specific process leading to infantile spasms. Detailed knowledge of this process would be a major step toward understanding the pathophysiology of infantile spasms itself, and a necessary first step toward devising a more effective therapy. In addressing such issues, consideration should also be given to the possibility of unique genetic factors common to infantile spasms patients which may interact with independent genetic and/or environmental factors as a critical step in the pathophysiological process.

Chapter 10

Pathophysiology

1. INTRODUCTION

The pathological findings that have been identified in patients with infantile spasms are diverse, and reflect the very large number of conditions which have been etiologically associated with this disorder. As reviewed in Chapter 9, and summarized in Table 9.2, these include a variety of genetic disorders, many with specific central nervous system malformations and/or metabolic dysfunctions, neoplasms, damage induced by toxic agents, trauma, hypoxic-ischemic changes, infections, vascular problems, and many conditions of uncertain or mixed origin. As was noted previously, at this time there is still uncertainty regarding most of these conditions in terms of a true causal relationship, as opposed to a coincidental association, and only a small fraction have been demonstrated to be true etiological factors. The focus of this chapter is, consequently, the search for pathological features and pathophysiological mechanisms that may be common to many of the identified potential etiological factors, and which may, therefore, provide clues to the underlying processes which result in the unique manifestations of infantile spasms. Unfortunately, very little solid evidence is available at this time, and it must be recognized that the basic cause of this disorder remains unknown. The absence of an adequate animal model of infantile spasms is a major limiting factor, and has significantly impacted the ability to directly investigate many of the unique features of this disorder. However, a number of hypotheses, based upon the available clinical, pathological and neurophysiological data, have been proposed, and will be reviewed.

2. NEUROPATHOLOGICAL OVERVIEW

2.1 Historical perspective

Early investigators recognized the apparent pathological diversity associated with infantile spasms, and speculation regarding possible critical abnormalities or a common denominator was frequent. In the second paper known to have been published on this disorder, Newnham (1849) theorized on these aspects, and concluded that a subcortical etiology, possibly involving the spinal cord or brainstem, seemed most likely, with cerebral dysfunction occurring later. More than a century later, in spite of renewed interest in the disorder, no significant progress had been made in identifying specific causative processes (see review by Lacy and Penry, 1976). Autopsy findings based on routine gross and histological examinations were remarkable only for the wide spectrum of abnormalities found, which, in various cases, included evidence for either cortical or subcortical pathology, or both, and documented the multiplicity of causative factors resulting from pre-, peri-, and postnatal insults. Such findings could not easily be reconciled with the very specific and unique ictal characteristics of infantile spasms. The only common factor seemed to be one of maturational status, with the disorder emerging in response to the various apparent etiological factors only during a limited time period of infancy.

Explanation of the pathological findings was further complicated in the early 1950s by the discovery of the unique EEG characteristics typically associated with this disorder. Hypsarrhythmia was an unusual and specific electrographic pattern, and seemed to imply a diffuse, or multifocal, abnormality of cortical function, which was difficult to reconcile with the very wide range of observed brain abnormalities, which could be focal, multifocal, or diffuse, and which could be cortical or subcortical, or both. In view of these known characteristics, it was suggested that involvement of both the cortex and diencephalon might be necessary for development of infantile spasms, and it was hypothesized that seizures might arise from an epileptogenic thalamic lesion, but only if it was disinhibited by simultaneously impaired cortical function (attributed to Gastaut and Roger [1953] by Kellaway [1959]) . Druckman and Chao (1955), on the other hand, felt that a brainstem site of seizure origin was most likely, commenting that the bilaterally synchronous nature of the spasms suggested that the discharge originated in midline structures, and that the position of the limbs in some spasms resembled decerebrate rigidity. Kellaway (1959) also favored a brainstem origin, pointing out that the characteristic seizures may continue without change after the EEG has normalized, thus making it unlikely that the cortex is essential to the pathophysiological process.

2.2 The search for unique structural abnormalities

While neuropathological investigations have still not identified any truly unique findings associated with infantile spasms, they have provided additional information relevant to the question of pathophysiology. It is clear, from the results of a number of autopsy findings, based upon conventional gross examination and histopathological studies, that infantile spasms can be associated with essentially any combination of cortical and/or subcortical pathology. Cases have been described in which there was evidence for cortical/cerebral lesions, but with no evidence for brainstem pathology (Trojaberg and Plum, 1960; Tucker and Solitare, 1963; Bignami et al., 1964; Branch and Dyken, 1979). Other studies have found evidence for widespread pathology involving various subcortical structures, including the brainstem, as well as the cerebrum (Sinton and Patterson, 1962; Bignami, 1966; Satoh et al., 1986; Tominaga et al., 1986; Morimatsu et al., 1972; Buchino et al., 1996). Still other cases have been described in which brainstem (and/or other subcortical) lesions were present, in the absence of apparent cortical pathology (Kellaway, 1959; Kamoshita et al., 1970; Tominaga et al., 1986). Finally, in an occasional case, the brain appears to be normal, with no evidence for either cortical or subcortical/brainstem pathology (Bignami et al., 1964; Jellinger, 1987).

Additional information relevant to the pathophysiology of infantile spasms has been obtained from case reports describing surgical removal of various well-circumscribed anatomical lesions. Excision of focal cerebral tumors (Branch and Dyken, 1979; Mimaki, et al., 1983; Ruggieri et al., 1989; Wyllie et al., 1996a), subtentorial/brainstem tumors (Dolman et al., 1981; Aktan et al., 1997), and porencephalic cysts (Palm et al., 1988; Uthman et al., 1991) have been described, and in most of these cases significant improvement of the patient's condition was observed. In all cases, the lesions were assumed to have been the basis of the patient's seizures, and, in support of this assumption, in several instances spasms that had been refractory to medical treatment ceased after surgery.

Spiegel et al. (1958) studied several patients with refractory epilepsy, including 5 with infantile spasms, by means of depth electroencephalography, and reported finding abnormal seizure discharges in the basal ganglia which showed variable temporal relationships to cortical discharges. In some instances, scalp and subcortical discharges were simultaneous, in others the scalp events preceded those in the depth, while in others the basal ganglia discharges preceded those in the cortex. A favorable effect of pallidotomy or pallidoamygdalotomy was reported, with control of seizures achieved in 4 of the 5 infantile spasms cases. These investigators suggested that the basal ganglia may play an important role in the mechanism of this disorder.

Following the report of Chugani et al. (1990) which described the successful application of resective surgery in several cryptogenic patients who showed focal metabolic abnormalities during positron emission tomography (PET), there has

been an increasing interest in this therapeutic modality in infantile spasms. Several groups have reported favorable outcomes following cortical resections, including seizure control (see Chapter 11, section 3) and possibly improved mental status (see Chapter 12, section 3.2.2). Additional information regarding the pathological processes associated with infantile spasms has subsequently been made available through examination of tissue resected during these surgical procedures (Adelson et al., 1992; Vinters et al., 1992; Lortie et al., 2002). This approach does not directly address the basic issue of the site of origin of the seizures, since the only tissue available is that selected for resection based on the results of diagnostic procedures (including PET and/or SPECT), but it has provided novel information regarding cortical pathology present in patients with infantile spasms, some of whom were classified as cryptogenic based upon clinical findings and routine imaging studies (CT/MRI). In a recent review and analysis of this topic, Vinters (2002) concluded that cortical dysplasia is the most common histopathological abnormality found in tissue resected from infantile spasms patients. This disorder of neuronal migration is characterized by a number of atypical features, including disordered lamination, blurring of the cortex-white matter junction, neuronal dysmorphism, irregular nodules of gray matter within the subcortical white matter region, as well as other abnormalities. In a study of 13 infants with infantile spasms who had resections of neocortical tissue, Vinters et al. (1992) reported that 9 (69%) had cortical dysplasia. Adelson et al. (1992) found that 5 of 7 patients (71%) treated surgically for infantile spasms had cortical dysplasia, and noted that in all 5 of these cases CT and/or MRI findings had been normal at the time of diagnosis, although all 5 did show regions of metabolic dysfunction on PET. In these studies, patients not showing cortical dysplasia did exhibit a wide variety of other pathology, such as reactive changes, encephalomalacia, and neurofibrillary changes. In some cases, multiple abnormalities were present. Hodozuka et al. (2000) have emphasized that resected tissue often shows evidence of hypervascularization, which they interpret as a dysplasia of vessels. These investigators noted such changes in several patients with infantile spasms, in association with cortical dysplasia and an oligoastrocytoma, and raised the possibility that vascular abnormalities may contribute to the epileptogenicity of the focal lesion.

The above diverse observations, based upon anatomical/structural examinations, appear consistent with two general, but contradictory, interpretations: 1) Infantile spasms is a non-specific, although time-limited, response, and can result from lesions located in widespread locations, cortical or subcortical, assuming that they are present at the appropriate maturational stage (Jellinger, 1970), or 2) A specific lesion is required for the development of infantile spasms (although its site and character are still unknown), but its nature is such that it may not be recognized in conventional neuropathological studies (e.g., the specific pathology could involve ultrastructural changes, metabolic dysfunction, or neurotransmitter/receptor pathology).

2.3 Ultrastructural abnormalities

There have apparently been very few studies in which the detailed, or ultrastructural, anatomy of the brain has been assessed in patients with infantile spasms, and contrasted with that present in normal subjects or patients with other neurological conditions. Huttenlocher (1974) applied a quantitative Golgi method to study the dendritic spread of pyramidal neurons in the frontal region of 5 children with severe mental retardation, 4 of whom had infantile spasms. In comparison to normal controls, as well as to several children with less severe mental deficits, all patients in the study group exhibited several abnormalities of dendritic development, including decreased length of the basal dendrites, fewer secondary branches, a decrease in the number of branches from the perikaryon, and a decrease in the number and length of the horizontal and tangential branches of apical dendrites. However, these changes were seen in the single patient without infantile spasms, as well as the 4 with this condition, and so the specificity of the findings was not established.

2.4 Biochemical disturbances

Infantile spasms has been associated with many metabolic disorders in sporadic case reports (Chapter 9, Table 9.2), and evidence suggesting a true causal relationship currently exists for two of these genetically-based conditions, phenylketonuria and pyruvate dehydrogenase deficiency. However, these specific conditions account for, at most, a very small fraction of infantile spasms cases, and clearly are not suitable candidates for a basic mechanism, or common denominator underlying all cases. Nevertheless, the possibility exists that dysfunction within some specific metabolic pathway could be triggered by multiple etiological factors, and be responsible for the unique seizures and EEG features of this disorder. This possibility has been explored in numerous investigations conducted over the past 50 years, and, while no dysfunction common to all cases has yet been discovered, the findings of these studies have provided significant information which is clearly relevant to the design of future studies, as well as to the assessment of current hypotheses regarding pathophysiology (Section 3, below).

2.4.1 Pyridoxine and tryptophan metabolism

Cochrane (1959; cited in Lacy and Penry, 1976, p 32) reported evidence for pyridoxine deficiency in 5 patients with infantile spasms, based upon the results of tryptophan loading tests. He also observed clinical and EEG improvement in these patients following therapy with large doses of pyridoxine (vitamin B_6). This study is of particular interest since it stimulated subsequent investigations of both pyridoxine and tryptophan metabolism in infantile spasms. The apparent

effectiveness of pyridoxine was intriguing because of its known role as a coenzyme in many metabolic pathways, including serotonin synthesis from 5-OH-tryptophan and GABA synthesis from glutamic acid, while tryptophan is the precursor of 5-OH-tryptophan, and, ultimately, serotonin. The tryptophan load test itself, which is used as a marker of pyridoxine deficiency, is based on another coenzematic role of pyridoxine. Tryptophan, in addition to its role as a precursor of serotonin (through 5-OH-tryptophan), is also a precursor of kynurenine, which normally follows a metabolic pathway to 3-OH-kynurenine, 3-OH-anthranilic acid, and nicotinic or quinolinic acids. However, the synthesis of 3-OH-anthranilic acid is pyridoxine-dependent, and in pyridoxine deficiency 3-OH-kynurenine is transformed by an alternative pathway to xanthurenic acid, which is then found in elevated amounts in the urine, especially after administration of tryptophan.

Bower (1961) evaluated 18 children with infantile spasms for evidence of pyridoxine deficiency using the tryptophan load test, and found that 6 of the 12 cryptogenic patients (50%) had abnormal results (increased urinary xanthurenic acid), while all 6 symptomatic patients in this study had normal findings. Ten patients (3 symptomatic, 7 cryptogenic) were subsequently treated with ACTH or corticosteroids, and in every case (including those previously within the normal range) there was a definite reduction of xanthurenic acid output when the tryptophan load test was repeated, with the values for all patients now falling within the normal range. Three cryptogenic subjects with initially elevated xanthurenic acid levels were subsequently treated with pyridoxine, and, while xanthurenic acid levels normalized in all cases, clinical improvement was noted in only one patient. The author concluded that there appears to be a disturbance of pyridoxine metabolism in some cryptogenic patients, and hypothesized that the efficacy of steroid therapy could be related to its effects on the maturation of enzyme systems which have been disturbed by various cerebral insults. Hellstrom and Vasella (1962) also found positive tryptophan load tests in a group of infantile spasms patients, but noted that since most cases are not corrected by administration of vitamin B_6, the disturbed tryptophan metabolism probably does not have a direct relationship to the seizure etiology. Coleman et al. (1971) reported elevated serum serotonin levels, as well as increased efflux of serotonin from platelets, in 3 of 5 infantile spasms patients, but, since treatment with antiserotonergic agents (see Chapter 11, section 2.3.4) was not successful, they felt that increased endogenous serotonin was unlikely to be the primary disease process.

A number of more recent studies have looked at the tryptophan metabolic pathway in more detail, and, while the results are not entirely consistent, the majority have indicated the presence of disturbed tryptophan metabolism in at least some infantile spasms patients. Yamamoto (1991) and Yamamoto et al. (1992) found decreased levels of serotonin in the CSF of infantile spasms patients in comparison to control patients, and decreased CSF levels of 5-HIAA, the major metabolite of serotonin, were noted in several investigations

(Silverstein and Johnston, 1984; Yamamoto, 1991; Langlais et al., 1991; Yamamoto et al., 1992). However, in two other studies 5-HIAA levels were reported to be similar in infantile spasms and control subjects (Ito et al., 1980; Airaksinen et al., 1992). Decreased CSF kynurenine levels have been found in several studies (Yamamoto, 1991; Langlais et al., 1991; Yamamoto et al., 1992; Takeuchi et al., 1999), although its major metabolite, 3-OH-kynurenine, was elevated in infantile spasms (Yamamoto, 1991; Yamamoto et al., 1992, 1994). Kynurenic acid (an alternative metabolite of kynurenine) was found to be decreased in two investigations (Yamamoto et al., 1994, 1995). ACTH treatment was reported to produce an increase of the previously decreased 5-HIAA levels in two studies (Langlais et al., 1991; Yamamoto et al., 1992), and was associated with a decrease of both kynurenine and 3-OH-kynurenine (Yamamoto et al., 1992). A role for disturbed tryptophan metabolism in infantile spasms was also suggested by the observation by Coleman (1971) that 9 of 60 Down's syndrome patients (15%) who were receiving 5-OH-tryptophan (for improvement of muscle tone) subsequently developed infantile spasms. Similar results were also reported by Airaksinen (1974) and Riikonen (1982). However, infantile spasms also occur spontaneously in a significant number of patients with Down's syndrome not treated with 5-OH-tryptophan (Chapter 9, section 3.2).

Evidence for decreased tryptophan expression in brainstem neurons (medullary raphe nuclei) was reported by Hayashi et al. (2000), who applied immunohistochemical techniques to tissue obtained at autopsy from 4 subjects with infantile spasms attributed to hypoxic-ischemic encephalopathy.

Considered as a group, the above findings suggest that a significant proportion of infantile spasms patients do have a disturbance of tryptophan metabolism, and that this dysfunction may be associated, at least in some cases, with a dysfunction of pyridoxine metabolism. It is, however, not possible to determine from the available information if this metabolic disturbance is an actual primary cause of infantile spasms, possibly as a result of direct neuromodulatory effects of some tryptophan metabolites and/or impaired serotonergic mechanisms as suggested by some investigators (e.g., Silverstein and Johnston, 1984; Langlais et al., 1991 Yamamoto, et al., 1995; Takeuchi et al., 1999), or if it is secondary to other mechanisms actually responsible for the disorder, as postulated by others (e.g., Hellstrom and Vasella, 1962).

2.4.2 Catecholamine metabolism

Relatively few studies have investigated catecholamine metabolism in infantile spasms patients. The average level of the major metabolite of norepinephrine, 3-methoxy-4-hydroxy-phenylethylene glycol (MHPG), was reported to be significantly decreased in the CSF of 7 patients with infantile spasms, in comparison to age matched controls, by Langlais et al. (1991), and this value did not increase following ACTH therapy. However, in an earlier

study of this metabolite, Ito et al. (1980) found no significant differences between patients and control subjects. Equally variable results have been reported for CSF levels of homovanillic acid (HVA), the major metabolite of dopamine. In comparison to control subjects, Langlais et al. (1991) found the levels in infantile spasms patients to be significantly decreased, Ito et al. (1980) and Ross et al. (1983) reported significant elevations, while Airaksinen et al. (1992) found no significant differences. Ito et al. (1980) reported that the elevation seen in his patients appeared to be related to the presence or absence of seizures, and found comparable elevations of HVA in patients with other seizure types within a few hours of seizure occurrence. In a study of 25 children with infantile spasms, Riikonen (1996a) found no differences in CSF HVA levels between cryptogenic and symptomatic patients.

On the other hand, evidence for decreased tyrosine hydroxylase (active enzyme for conversion of L-tyrosine to L-dopa) expression in brainstem neurons (mesencephalon, locus ceruleus, dorsal vagal nucleus) was reported by Hayashi et al. (2000), who applied immunohistochemical techniques to tissue obtained at autopsy from 8 subjects with infantile spasms attributed to lissencephaly and hypoxic-ischemic encephalopathy. However, as noted by the authors, these post-mortem studies were conducted several years after spasms had ceased, and all subjects had evolved to the Lennox-Gastaut syndrome.

In view of these results, it must be concluded that insufficient information is currently available to clearly establish a role for disturbed catecholamine metabolism as a primary factor underlying infantile spasms.

2.4.3 Amino acid metabolism

Amino acid levels in the CSF of patients with infantile spasms have been assessed in several studies (Table 10.1). Honda (1984) measured the CSF levels of 17 amino acids in 10 patients (Table 10.1, A), and, prior to treatment, found significantly reduced levels of asparagine, isoleucine, leucine, tyrosine, phenylalanine, ornithine, lysine, and histidine. Following treatment with ACTH the pattern was altered, with relative increases of asparagine, glutamine, glycine, alanine, phenylalanine, lysine and arginine. The author noted that altered amino acid levels were also observed in patients with other seizure disorders, although the patterns were different from those seen in the infantile spasms patients. In a similar study, Spink et al. (1988) assessed the CSF levels of 14 amino acids in 12 patients, but observed a considerably different pattern, with significant elevations of lysine and glutamate occurring in symptomatic patients only (Table 10.1, B). Levels of the other amino acids did not differ significantly from the control group in symptomatic patients, and all levels in the cryptogenic group were similar to the controls. These authors felt that it was most likely that the abnormal amino acid levels observed in the symptomatic patients were related to various underlying disorders rather than to infantile spasms. Tekgul et al. (1999) evaluated the effect of ACTH treatment on the CSF levels of 17 amino acids in 8

***Table 10.1* CSF amino acid levels in patients with infantile spasms**
Comparison of 3 studies

Amino acid	*Pre-treatment**			*Post-treatment change***		
	A	*B*	*C*	*A*	*B*	*C*
4-hydroxy proline						–
Alanine	–	–		↑		–
Arginine	–	–		↑		–
Asparagine	↓	–		↑		
Aspartate		–				↑
Cysteine						–
Glutamate		↑				–
Glutamine	–	–		↑		
Glycine	–			↑		–
Histidine	↓			–		
Isoleucine	↓	–		–		–
Leucine	↓	–		–		–
Lysine	↓	↑		↑		–
Methionine	–			–		–
Ornithine	↓	–		–		
Phenylalanine	↓	–		↑		–
Proline						–
Serine	–	–		–		–
Taurine	–			–		
Threonine	–			–		–
Tryptophan		–				
Tyrosine	↓	–		–		–
Valine	–			–		–

* comparison to control infants

** change following treatment compared to pretreatment value

↑ level significantly elevated

↓ level significantly decreased

– level not significantly different

A: Honda, 1984 B: Spink et al., 1988 C: Tekgul et al., 1999

patients with infantile spasms (Table 10.1, C), and found that a significant change occurred only with the aspartate level, which was significantly increased compared to the pretreatment value.

The excitatory amino acids glutamate and aspartate were specifically evaluated in 13 untreated patients with infantile spasms by Ince et al. (1997). They found that the average aspartate level was significantly elevated in the

patients (in comparison to age-matched controls), while glutamate values were within the normal range. High aspartate values were observed in both cryptogenic and symptomatic patients, although there were some infantile spasms patients with normal values. They speculated that aspartate, an excitatory and neurotoxic neurotransmitter, might have a role in triggering spasms.

Significantly decreased CSF levels of the inhibitory amino acid γ-aminobutyric acid (GABA) have been reported in several studies of infantile spasms (Ito et al., 1984; Loscher and Siemes, 1985; Kurlemann et al., 1997). The lowest levels have been observed in symptomatic patients (Airaksinen et al., 1992; Riikonen, 1996a) as compared to the cryptogenic groups. Kurlemann et al. (1997) reported that GABA levels increased into the normal range in a patient who responded favorably to vitamin B_6 therapy, while Ito et al. (1984) found that CSF GABA levels decreased further in 8 patients who responded to ACTH and were seizure-free. Thus, while these findings are suggestive of disturbed GABA metabolism in some infantile spasms patients, there is not a clear relationship between GABA levels and the occurrence of spasms.

Ohtsuka et al. (1983) found elevated CSF levels of homocarnosine (a dipeptide of GABA and histidine) in 5 of 8 (63%) infantile spasms patients, and observed that in all cases the values declined into the normal range following attainment of seizure control with ACTH therapy.

The divergent fndings of the studies reviewed above do not argue convincingly for a primary role of amino acid metabolism in the pathogenesis of infantile spasms, although altered function in some of these metabolic pathways is clearly present in a subset of these patients.

2.4.4 Neuropeptide metabolism

Because of the demonstrated efficacy of ACTH and corticosteroids in infantile spasms, the possibility that dysfunction within the hypothalamic-pituitary-adrenal hormonal system could be a crucial element in the pathophysiology of this disorder has been suspected by many investigators. In a direct test of this possibility, Rao and Willis (1987) administered metyrapone to 10 infants with infantile spasms (5 symptomatic and 5 cryptogenic). Metyrapone selectively inhibits 11-β-hydroxylase, an enzyme necessary for cortisol synthesis from cholesterol, and, in the presence of normal hypothalamo-pituitary-adrenal function, serum cortisol levels are decreased, while release of both ACTH and 11-deoxycortisol are increased. In this study 9 of the 10 infantile spasms patients (90%) showed a normal response prior to treatment, while one had a mildly decreased ACTH response, suggesting diminished pituitary function. These investigators also documented normal pretreatment serum levels of cortisol, ACTH and 11-deoxycortisol in all 10 patients.

However, studies of CSF neuropeptides in infantile spasms patients have revealed a number of atypical characteristics. In comparison to age-matched

control groups, the average CSF levels of ACTH are significantly lower in groups of infantile spasms patients (Facchinetti et al., 1985; Nalin et al., 1985; Baram et al., 1992a, 1995; Nagamitsu et al., 2001). This abnormality was found to be most pronounced in cryptogenic patients in one study (Nalin et al., 1985), while in two other investigations symptomatic patients had the lower ACTH values (Riikonen, 1996a; Heiskala, 1997), and in one study there was no difference between groups (Baram et al., 1995). CSF cortisol levels were also reported to be significantly reduced in infantile spasms patients in one study (Baram et al., 1995).

Less consistent findings have been reported for the CSF levels of β-endorphin, which is derived from the same precursor molecule (propiomelanocortin) as ACTH. Most investigators have reported normal CSF levels of this peptide (Facchinetti et al., 1985; Nalin et al., 1985; Gillberg et al., 1990), although Nagamitsu (1993; Nagamitsu et al., 2001) found values significantly lower than those of age-matched controls.

The CSF levels of corticotropin-releasing hormone (CRH), a peptide which promotes pituitary ACTH release, did not differ significantly from control values in two studies of infantile spasms patients (Baram et al., 1992a; Nagamitsu et al., 2001). Similarly, the CSF levels of interleukin-1-beta, which is involved in CRH synthesis, did not differ significantly from control values (Baram et al., 1992a). Evidence for increased activity of somatostatin, a hypothalamic peptide with known excitatory effects, in the CSF of infantile spasms patients was reported in two studies (Nagaki et al., 1988; Hirai et al., 1998), with normalization occurring after administration of pyridoxal in one group (Hirai et al., 1998). In a post-mortem study using immunohistochemical analysis, Hayashi et al. (2000) reported decreased levels of parvalbumin and methionine enkephalin in brainstem areas of infantile spasms patients. The pretreatment CSF levels of prolactin were found to be significantly elevated in a group of 15 infantile spasms patients, as compared to age-matched control subjects in a study by Aydln et al. (2002), and rose still higher after therapy (ACTH and Vitamin B_6).

The findings of these studies investigating neuropeptide alterations in infantile spasms, while divergent in some areas, do provide considerable evidence supporting a role of the hypothalamo-pituitary-adrenal axis in the pathogenesis of infantile spasms. This possibility is further strengthened by the evidence indicating efficacy of ACTH and corticosteroid therapy in this disorder.

2.4.5 Miscellaneous findings

Neuron-specific enolase, considered to be a marker for neuronal injury, did not differ significantly in either serum or CSF between infantile spasms patients and controls (Suzuki et al., 1999a). Measures of oxidative metabolism, including **pH**, **phosphocreatine/ATP ratio**, and **phosphocreatine/inorganic phosphate ratio**, were found to be similar in infantile patients and controls, and ACTH treatment did not change the patterns (Yoshioka, et al., 1994). Feng et al. (1991)

tested hair samples of 23 patients with infantile spasms for the trace elements **calcium, iron, copper, zinc and lead**, and reported significantly increased levels of calcium and zinc and decreased levels of lead, in comparison to a normal control group. CSF levels of gangliotetraose-series **gangliosides**, which are involved in the neuronal maturation process, were significantly decreased in a group of 14 infantile spasms patients, in comparison to age-matched disease controls (Izumi et al., 1993), and this relationship was found in both cryptogenic and symptomatic patients. Serum and CSF **lactate** and **pyruvate** levels were within the normal range in a group of 12 infantile spasms patients prior to ACTH therapy, and both levels were significantly increased following treatment (Miyazaki et al., 1998). An analysis of CSF proteins in a group of 50 infantile spasms patients indicated evidence for an increased permeability of the blood-CSF barrier, particularly for **albumin** (Siemes et al., 1981, 1984). These changes were most pronounced in the symptomatic group, and minimal in cryptogenic patients. The permeability normalized following ACTH or corticosteroid treatment. Riikonen et al. (1997) measured levels of **nerve growth factor** in the CSF of 38 infantile spasms patients (6 cryptogenic, 32 symptomatic). While all cryptogenic patients had normal levels, 17 symptomatic patients (non-infectious) had no detectable level, and 5 symptomatic subjects (all post-infection) had significantly elevated levels. Elevated CSF levels of **nitric oxide** metabolites, nitrates, and nitrites (considered to reflect brain nitric oxide production) were found to be significantly elevated in symptomatic patients with infantile spasms, while levels in cryptogenic patients did not differ significantly from the control group (Vanhatalo and Riikonen, 2001). Similar elevations of CSF nitric oxide metabolites, as well as reduced levels of **insulin-like nerve growth factor**, were found in patients with the PEHO syndrome (see Chapter 9, section 3.2).

While insufficient information exists to permit a meaningful assessment of the above findings, in most instances it appears likely that the observed changes associated with infantile spasms reflect underlying brain damage rather than indicators of the basic pathological processes.

2.5 Brain maturation

While most cases of infantile spasms occur within the first year of life, and provide support for the commonly accepted belief that this disorder is critically dependent upon an interplay of factors producing brain damage with the ongoing developmental processes of the central nervous system, an occasional case appears to contradict this requirement. For example, we reported two cases of infantile spasms with hypsarrhythmia that occurred in older children following near-drowning episodes. In both cases, the causative event occurred well after the first year of life (16 and 31 months). A similar case was reported by Ganji et al. (1987) in a patient who had been normal prior to the near-drowning episode at 13 months. In addition, Maton et al. (2000) recently reported the occurrence of

epileptic spasms, with many features suggestive of infantile spasms, in a 69 year old male following an encephalopathy of unknown origin that was associated with prolonged coma. The patient's condition improved dramatically and spasms ceased following treatment with corticosteriods. Finally, the myoclonic events and associated ictal EEG changes seen in older children with subacute sclerosing panencephalitis are very similar to those seen in infantile spasms patients. Also, as is the case with infantile spasms, such clinical and ictal changes may be seen when the background EEG is normal (Hrachovy, unpublished observations). These findings suggest that while maturational factors clearly play a role in the pathophysiology of infantile spasms, under some circumstances these factors may be overridden, permitting certain features of the disorder to be expressed well outside of the usual time window.

2.6 Evidence based on genetic analysis

Genetic factors are unquestionably involved in a large proportion of infantile spasms cases. As discussed in Chapter 9 (section 3.2), at least 91 specific genetically-based entities have been identified as occurring in association with infantile spasms in published reports. While some of these associations may be coincidental, of the 16 pathological entities of all types listed in Table 9.3 for which available statistical evidence supports a true causal relationship with infantile spasms, 12 have a definite genetic basis. Consequently, the application of genetic analysis techniques to the study of pathogenesis offers the possibility of providing novel information regarding underlying developmental and metabolic elements which may be required for the expression of this disorder. While relatively few studies have applied these methods to infantile spasms, several reports have provided evidence demonstrating the potential value.

Studies related to the X-linked infantile spasms syndrome have demonstrated evidence suggesting that common elements may underlie several clinically distinct entities that have been associated with infantile spasms. This familial disorder was described by Feinberg and Leahy (1977), and is characterized by mental retardation and infantile spasms, which typically occur without evidence for other etiological factors. DNA mapping has implicated a region in the distal portion of the short arm of the X chromosome (Xpter-Xp11) in several studies investigating this syndrome (Claes et al., 1997; Bruyere et al., 1999; Stromme et al., 1999, 2002; Scheffer et al., 2002; Turner et al., 2002). These findings are particularly relevant since chromosomal defects in this same general region of the X chromosome have been implicated in several of the other disorders that have been causally associated with infantile spasms. Aicardi syndrome (agenesis of the corpus callosum, ocular abnormalities, and infantile spasms), has been associated with X chromosome abnormalities near locus Xp22 (Ropers et al., 1982; OMIM #304050), possibly involving autosomal translocation. A subset of patients with the neurocutaneous syndrome hypomelanosis of Ito, originally identified as incontinentia pigmenti type 1, also have abnormalities in this same

region, with evidence for X/autosomal translocations at Xp11 (Hodgson et al., 1985; OMIM #300337). Finally, the E1-alpha subunit gene for pyruvate dehydrogenase complex deficiency, a metabolic disorder associated with congenital lactic acidemia, has been localized to Xp22.1-Xp22.2 (Borglum et al., 1997; OMIM #312170), a site also within the region associated with X-linked infantile spasms. Thus, all four of these conditions – Aicardi syndrome, hypomelanosis of Ito (some patients), pyruvate dehydrogenase deficiency, and X-linked infantile spasms – are associated with infantile spasms, although other clinical features differ greatly, and are also associated with similar chromosomal defects on chromosome X. This suggests the possibility that all of these conditions could involve a closely linked gene located within the involved region of the X chromosome, and that the product of that gene could play a crucial role in the pathophysiology of infantile spasms.

In a recent investigation, Heilstadt et al. (2001) studied 24 patients with the chromosome 1p36 deletion syndrome, and reported that 12 subjects had epilepsy, including 3 with infantile spasms. It was further determined that the deletion included the locus of the potassium channel β-subunit gene (KCNAB2) in 9 of the 24 patients, while the gene was retained in the other subjects. The incidence of epilepsy was higher in the KCNAB2 deleted group (89%), which included all three of the infantile spasms patients, than in those with the intact gene (27%). Since absence of the β-subunit gene would be expected to increase neuronal excitability by a reduction of membrane repolarization, the authors suggested a possible relationship between this gene and seizure development. These findings raise the possibility that similar mechanisms could be involved in other genetic disorders associated with infantile spasms, and that more than one gene could influence neuronal excitability. This possibility is supported by the work of Crino (2002) whose group has found evidence for increased expression of several glutamate receptor subunits, as well as decreased expression of several inhibitory subunits (e.g., $GABA_{A\alpha 1}$ and $GABA_{A\alpha 2}$) in studies of tuberous sclerosis and cortical dysplasia, both conditions associated with infantile spasms as well as other seizure types.

2.7 Immune system dysfunction

The possibility that infantile spasms could be a result of abnormal immune system function was proposed nearly forty years ago (Mandel and Schneider, 1964; Martin, 1964). Evidence supporting this concept at that time included the recently discovered efficacy of ACTH and corticosteroids (Sorel and Dusaucy-Bauloye, 1958), agents known to influence the immune system, as well as a report by Reinskov (1963) demonstrating the presence of antibodies to normal brain tissue in the sera of several patients with infantile spasms. Subsequent investigations have provided additional information suggesting the presence of altered immune mechanisms in some patients, although the results have not always been consistent.

In a study of 14 patients with infantile spasms, Mota et al. (1984) found elevated levels of an antibrain antibody in all cases, confirming the earlier results of Reinskov (1963), and concluded that the findings were indicative of an autoimmune response. A significant reduction of T lymphocytes was reported by Montelli et al. (1984) in 10 of 18 infantile spasms patients (55%), with no apparent alteration of the B lymphocytes, and all 18 patients showed depression in at least one of 5 tests of cellular immunity that were administered. In addition, decreased levels of IgG, IgA, and IgM were found in 10% of the subjects. However, we were unable to confirm these findings in a group of 7 patients (Hrachovy et al., 1985). Our analysis did, however, identify increased activation of B lymphocytes in 6 of the 7 patients, and in a subsequent study, elevated numbers of a subset of helper T cells were identified (Hrachovy et al., 1988a). Benson et al. (1987) reported that a subset of their infantile spasms patients had an elevated IgG index (a comparison of ratios of CSF and serum IgG to similar ratios of CSF and serum albumin), which is a measure of intrathecal immunoglobulin synthesis, and suggested that immunological mechanisms might contribute to the pathogenesis in some cases. However, Haraldsson et al. (1992) noted that while serum IgG levels were elevated in a group of patients with infantile spasms or Lennox-Gastaut syndrome (in comparison to a normal control group), the findings did not differ significantly from patients with other forms of epilepsy.

No detectable levels of CSF interferon-alpha were found in 12 infantile spasms patients evaluated by Dussaix et al. (1985), while, in the same study, many patients with infectious encephalitis or lupus did have significant levels. On the other hand serum interferon-alpha, as well as interleukin-2 and tumor necrosis factor-alpha, were significantly elevated in a group of 23 infantile spasms patients (in comparison to healthy control subjects) in a study conducted by Liu et al. (2001). These cytokines were elevated in both cryptogenic and symptomatic subjects, although the levels were significantly higher in the symptomatic group. These authors interpreted the findings as evidence for immune system activation, and suggested that cytokine imbalance could be involved in the genesis of infantile spasms, noting that interleukin-2 is known to increase neuronal excitability, while tumor necrosis factor-alpha can potentiate the excitotoxic activity of glutamic acid.

No differences in the class I HLA antigens (A, B, and C) were demonstrated between a group of 19 infantile spasms patients and normal subjects in a study conducted by Howitz and Platz (1978). We (Hrachovy et al., 1988a) confirmed these negative findings in a group of 29 patients, but did find a significant increase of the DRw52 antigen (a class II molecule), which was present in 90% of the infantile spasms group, as compared to 72% of controls. In addition, 3 of 12 white patients in this study had the complete B18, DR3 (DRw52) haplotype, whereas none of the 150 white controls had this pattern which has been associated with autoimmune disorders. In a study of 11 familial cases from 9 families (all patients had one or more siblings with infantile spasms), Howitz

(1980) found the HLA-A2 antigen in all of the patients, in contrast to only 54% of the normal controls. In a recent assessment of HLA antigens in 65 patients, Suastegui et al. (2001) documented a significant increase of the DR17 antigen, and a significant decrease of the DQ6 antigen, in the patients, as contrasted with normal subjects. Thus, several investigations have found different HLA antigen patterns in infantile spasms, although the specific types were not uniform across the studies. The reason for this discrepancy is unknown, but, since these studies were conducted on different population groups (United States, Denmark, and Mexico), they may reflect unique genetic characteristics.

Additional evidence suggesting an involvement of the immune system in this disorder is provided by the apparent efficacy of immunoglobulin therapy. As discussed in Chapter 11 (section 2.3.3), several studies have reported a favorable response to this treatment (pooled human immunoglobulin, largely IgG) in significant numbers of patients (response rates of 33-82%). No information is available regarding the mechanism by which such therapy modifies the underlying pathophysiological process. Van Engelen et al. (1994) have suggested that immunoglobulin may have a neuromodulatory effect, based upon previous animal studies that have demonstrated anticonvulsant properties.

While the above findings suggest that immune system function is altered in a subset of infantile spasms patients, it is still not known whether these findings signify a causal relationship, or simply reflect underlying responses to non-specific brain damage.

3. PATHOPHYSIOLOGICAL HYPOTHESES

The findings reviewed in the preceding sections, when considered together with the clinical characteristics of infantile spasms (Chapter 4), the neuroimaging data (Chapter 6), as well as the response to therapy (Chapter 11), present a confusing picture with respect to pathophysiology. Because this disorder has been associated with so many pathological conditions, both structural and biochemical, many investigators have concluded that the triggering factor is non-specific, but effective only within a narrow time window of brain development. On the other hand, the very stereotyped picture presented clinically in this disorder, as well as the unique electroencephalographic features, argue that, at least at some point in the pathophysiological pathway, there are common elements. In spite of many years of investigation into these questions, the common denominator, or final common pathway leading to infantile spasms, if one exists, is not evident, and, thus far, no mechanism capable of incorporating the diverse evidence into a comprehensible explanation of the basic cause of this disorder has been proven to exist. The available information regarding etiology and pathology (much of which has been reviewed above), the clinical features, and the response to therapy, have, however, suggested a number of hypotheses, or hypothetical models, to explain the pathophysiological mechanism of this

disorder. A number of these are summarized below, and discussed with respect to supporting evidence and limitations.

3.1 Brainstem origin

As noted above (section 2.1), even early investigators suspected that subcortical regions, including the brainstem, were crucially involved in the pathophysiology of this disorder. One clinical factor suggesting this is the common observation that the epileptic spasms have a unique, highly recognizable, character, and typically appear very similar in symptomatic patients who have markedly different patterns of cortical/cerebral damage. Unlike partial seizures, the character of the spasm itself infrequently provides any clue to the extent or location of affected cortical or subcortical regions. Another observation suggesting a subcortical origin is that the hypsarrhythmic EEG pattern characteristic of this disorder often exhibits an evolution over time to an entirely different pattern, and occasionally may normalize, at a time when the patient is still experiencing spasms similar in character to those seen at the onset. More direct evidence implicating brainstem structures is the fact that a number of cases have been described in which epileptic spasms apparently identical to those seen in infantile spasms have occurred in association with hydrancephaly and a complete absence of cerebral cortex (e.g., Neville, 1972; see Table 9.2, Chapter 9). Numerous other studies, making use of both pathological examination and imaging techniques, have provided substantial evidence indicating that the brainstem, and other subcortical regions, are frequently abnormal in infantile spasms patients (section 2, above)

Consideration of this evidence suggesting brainstem involvement, together with additional observations of the sleep patterns in infantile spasms patients (Hrachovy et al., 1981), led us to propose a pathophysiological model postulating a disruption of neuronal function within the pontine reticular formation as the primary defect in this disorder (Hrachovy and Frost, 1989a). The sleep pattern of patients with infantile spasms is typically disturbed, usually exhibiting a low total sleep time as well as a specific reduction in the percentage of stage REM (Chapter 5, section 4). This pattern suggests a disruption of the normal reciprocal relationship existing between the inhibitory noradrenergic and serotonergic neurons of the locus ceruleus and dorsal raphe, respectively, and the excitatory cholinergic neurons in adjacent regions, which is involved in the timing of REM sleep (Hobson et al., 1976). Specifically, a relatively decreased output of the cholinergic system, which appears to initiate and maintain the REM cycle was postulated, and could result from increased activity of the inhibitory system (noradrenergic and/or serotonergic), or damage to the cholinergic neurons. According to this model, the clinical seizures would result from phasic interference of descending brainstem pathways that control spinal reflex activity, thereby producing transient alterations of muscle activity manifested as motor spasms. Ascending pathways from these same brainstem areas project widely to

the cerebral cortex, and disturbed function could consequently result in the characteristic EEG changes, as well as disturbances of cognitive function. Because this brainstem region receives inputs from both higher and lower levels, the function of the abnormal system could be influenced by multiple factors.

In support of this model is considerable evidence from the studies reviewed above (sections 2.4.1 and 2.4.2) which have documented disturbed monoamine metabolism within the central nervous system of patients with infantile spasms. Animal studies have demonstrated that both ACTH (Pranzatelli, 1989) and corticosteroids (Nausieda et al., 1982) have suppressive effects on central serotonergic activity, suggesting that the efficacy of these agents in infantile spasms is consistent with the brainstem model. Abnormalities of brainstem evoked potentials (BAEPs) have been detected in some, but not all, infantile spasms patients (Chapter 5, section 5) and, consequently, provide only limited support for this hypothesis. However, it is of interest that in one study (Curatolo et al, 1989) abnormal BAEPs were found in a number of cases in which there was no brainstem abnormality detected by MRI.

A basic limitation of this model is the fact that, since the brainstem receives inputs from widespread brain areas, the observed changes in sleep characteristics in infantile spasms could be secondary to a pathological process located in some other region. In support of this possibility, it is known that a number of medical conditions are associated with altered sleep patterns, including REM suppression. In order to test the validity of this model, in subsequent studies we evaluated the effects of several drugs with known effects on monoamine metabolism. If the model is valid, agents which block the production, or reduce the effectiveness, of serotonin and norepinephrine would be expected to normalize the postulated pontine dysfunction. Initially, 12 patients with infantile spasms were treated with tetrabenazine, a drug which results in depletion of monoamines, and thus has both antiserotonergic and antiadrenergic properties. After 3 weeks of therapy, none of the patients showed cessation of spasms, and no improvement was observed in EEG characteristics or developmental skills (Hrachovy et al., 1988b). In a subsequent study involving 24 patients, the efficacy of methysergide, a serotonin receptor blocker, and α-methylparatyrosine (AMPT), which decreases the production of norepinephrine by competitively blocking tyrosine hydroxylase, were evaluated (Hrachovy et al., 1989). Only two of 12 patients (17%) receiving methysergide and 1 of 12 (8%) patients receiving AMPT for 3 weeks responded with cessation of seizures. Consequently, these studies did not provide strong support for the proposed model, and argue against this mechanism as a common denominator underlying infantile spasms. However, as Chugani et al. (1992) have pointed out, there are multiple types of serotonin receptors in the brain, and the agents we used are not specific for some of these types, thereby leaving open the possibility more specific antagonists might have a more definitive effect.

In addition, the possibility that predominantly impaired or depressed cholinergic function, rather than elevated monoamine activity, could be the

primary defect underlying the brainstem dysfunction is also consistent with the proposed model, but remains untested. This possibility is, in part, supported by the work of Rektor et al. (1987, 1990) who examined the acute effects (10-20 min) of physiostigmine (a cholinesterase inhibitor, which results in increased cholinergic activity) and atropine (a cholinergic receptor antagonist, which results in decreased cholinergic activity). They reported that physiostigmine significantly decreased paroxysmal EEG activity (including hypsarrhythmia in some cases) with relative normalization of the background pattern, while atropine had the opposite effect, and increased the abnormal activity. A more prolonged treatment period would be required in order to adequately test this aspect of the model, and to determine the effect upon spasm frequency.

3.2 Cortical – subcortical interactions

In spite of the extensive evidence for brainstem disturbance in infantile spasms, there have been many reports documenting the occurrence of this disorder in patients with cortical lesions and no evidence of brainstem involvement (section 2.2). As reviewed in Chapter 9, infantile spasms has been associated with discrete cortical lesions, including tumors and infarctions, which would not be expected to influence brainstem structure or neurochemical function. In an attempt to reconcile such findings with the evidence for brainstem involvement suggested by the clinical and electrographic findings, early investigators proposed that involvement of both the cortex and diencephalon might be required, and postulated that the seizures were initiated in an epileptogenic thalamic lesion, but only when it was disinhibited or released by simultaneously impaired cortical function (see section 2.1, above). A similar hypothesis was proposed by Wright (1969), who, after considering data from both human cases and myoclonic seizures in animals, concluded that the seizures may be a manifestation of abnormal activity in subcortical regions as part of a general release phenomenon resulting from a lack of neuronal input to the subcortical sites. While other investigators have also speculated that such cortical-subcortical interactions could be important in the pathogenesis of infantile spasms, until recently there was no experimental evidence to support the claims.

Following the first application of positron emission tomography (PET) to the study of infantile spasms by Chugani et al (1990, 1992), this group proposed a comprehensive pathophysiological model of infantile spasms which was based on a specific interaction of cortical and subcortical neuronal populations. This model incorporated the novel PET findings, summarized in Chapter 6, as well as other prior work relating to the clinical and pathological characteristics of this disorder. The model is based on several key observations derived from the PET studies, including evidence in many patients for focal or regional metabolic abnormalities, even in cryptogenic cases with normal CT/MRI studies, significantly increased metabolic activity in the lenticular nuclei bilaterally in the

majority of subjects, a suggestion of increased metabolic activity in the brainstem in some patients, and the finding that seizures were controlled in several patients following surgical resection of the cortical focus identified by PET. Chugani et al (1992; Chugani, 2002) propose that the primary dysfunction in infantile spasms is a focal or diffuse cortical abnormality which (at a critical maturational stage), triggers (through subcortical projection pathways) abnormal functional activity within the serotonergic neuronal population of the brainstem raphe nuclei. Activation of the raphe-striatal pathway is postulated as the cause of the observed hypermetabolism within the lenticular nuclei and brainstem, while raphe-cortical, and cortico-cortical, projections could be responsible for the hypsarrhythmic EEG pattern. According to this model, the epileptic spasms themselves would result from projections of the activated brainstem regions to spinal cord neurons, as well as from the lenticular activation.

This model incorporates much of the evidence reviewed above (section 3.1) for the brainstem hypothesis, including evidence for disturbed serotonin metabolism in infantile spasms and the involvement of the raphe region in sleep cycle control, which would account for the observed sleep disturbances in infantile spasms. The crucial difference is the primacy of the cerebral cortex in this model, and the abnormal activity within the raphe system is postulated to be secondary to epileptic discharges arising within dysfunctional cortical areas. This model, consequently, provides an explanation for prior observations of infantile spasms occurring in patients with lesions apparently confined to the cortex, as well as for the resolution of seizures and improvement of the EEG following surgical resection of cortical lesions (Chugani et al, 1990; Uthman et al., 1991; Wyllie et al., 1996b), since removal of the lesion would interrupt the sequence and permit resumption of normal brainstem function. The model is also consistent with the observed correlation between the onset age of infantile spasms in patients with cortical lesions, and the normal posterior-to-anterior maturational sequence of the cortex (Chapter 6), with onset tending to occur earlier with posterior lesions, since such a relationship would not be expected if the brainstem was the primary site.

Additional evidence in support of a cortical origin for infantile spasms has been provided in a number of recent studies. Pinard et al. (1993) described two cryptogenic cases in which hypsarrhythmia became unilateral, and spasms asymmetrical, following callosotomy, suggesting a corticocortical pathway was crucial for the generalization of hypsarrhythmia. Viani et al. (1994a) reported a case in which infantile spasms occurred following surgical excision of a neuroectodermal tumor, suggesting that a disturbance of cortical circuitry produced a functional alteration of subcortical mechanisms. In a study of 21 patients with periventricular leukomalacia, Okmura et al. (1996) found that all 6 children who subsequently developed infantile spasms and hypsarrhythmia had initial EEGs (within the first year of life) characterized by parieto-occipital polyspike and wave activity, while none of the 12 patients without such activity developed hypsarrhythmia or spasms, suggesting that cortical lesions were

involved in the genesis of this condition. Panzica et al (1999) used quantitative EEG analysis to examine the EEG characteristics immediately preceding seizure onset in 18 children with infantile spasms. An asymmetric EEG pattern preceded both symmetric and asymmetric motor spasms in 13 (72%) patients, suggesting a localized cortical origin.

Following the suggestion of Yamamoto et al. (1988), several investigators have pointed to the apparent coupling of partial seizures and infantile spasms in some patients (see Chapter 8, section 3.2) as evidence in support of a cortical-brainstem interaction hypothesis, suggesting that a partial seizure originating in the cortex could trigger a spasm in the brainstem (Donat and Wright, 1991b; Chugani et al., 1992; Carrazana et al., 1993). However, this possibility needs additional investigation, since statistically significant coupling of infantile spasms and partial seizures appears to be rare (Hrachovy et al., 1994a). The occurrence of infantile spasms in cases of hydrancephaly (Chapter 9, Table 9.2) is also difficult to reconcile with this model, since, in the absence of cortical tissue, the proposed epileptogenic input to the raphe is missing. In these, and some other cases lacking evidence for cortical dysfunction, it is necessary to implicate a primary brainstem lesion which interferes with normal raphe activity (Chugani et al., 1992). The findings of some recent PET studies are also not entirely consistent with the idea of a primary cortical lesion as the basis for infantile spasms. As reviewed in Chapter 6, a number of investigators have reported that a significant number of focal cortical metabolic abnormalities are transitory or variable over time, suggesting that not all such foci reflect an anatomically distinct lesion, and may instead be functional, and reflect some other causative factor, or input from some other brain region.

Dulac et al. (1994) have proposed a pathophysiological hypothesis generally similar to the model described above (Chugani et al, 1992). They suggest that spasms arise in subcortical structures such as the basal ganglia, probably as a result of functional deafferentation or disinhibition caused by continuous abnormal cortical activity, while the hypsarrhythmic EEG pattern directly reflects the cortical dysfunction. They believe that there is likely to be a combination of both focal and generalized factors, as well as a combination of cortical and subcortical mechanisms. Citing the observed relationship between the onset time of infantile spasms and cortical maturation patterns (see Chapter 6), Dulac (2001) suggests that the abnormal cortical activity that is postulated to be the primary triggering mechanism for infantile spasms could be caused by age-related hyperexcitability linked to developmental factors throughout infancy. Avanzini et al. (2002) also favor a mechanism based on cortical-subcortical interaction, and point out the similarity of the seizures associated with infantile spasms and the normal Moro reflex. They propose that a discharge originating from some region, such as the cortex, could activate, either by a triggering effect or through disinhibition, the supposed brainstem generator of this age-specific reflex.

Lado and Moshe (2002) have proposed another mechanism to explain the origin of infantile spasms, also based on the general concept of cortical-subcortical interaction. It is postulated that proconvulsant changes are necessary in both cortical and brainstem regions in order for the condition to develop, and they describe two basic possibilities: In one, increased cortical excitability is present, together with impaired regulation of the cortex by subcortical structures, thereby allowing the cortical epileptogenicity to be expressed, while in the other there is increased excitability in the brainstem, with inefficient descending cortical modulation, permitting expression of the brainstem epileptogenicity. In this model, the basic requirement is increased epileptogenicity in one area (cortex or brainstem), with concurrent failure of the other region (brainstem or cortex) to suppress the epileptic activity. In support of this hypothesis, they review prior studies in animals which have implicated the substancia nigra pars reticulata (SNR) in the regulation of such cortical-subcortical interactions, and emphasize that the SNR has been shown to mediate both anticonvulsant and proconvulsant effects. In addition, they cite evidence that the SNR is less effective in controlling epileptogenesis in the immature animal than it is in the adult. While no evidence in support of this model based on human studies has been published, it does provide a plausible explanation for why some infants with specific lesions or conditions develop infantile spasms, while other infants with apparently similar pathology do not.

3.3 Hypothalamic-pituitary-adrenal axis dysfunction

As reviewed above (section 2.4.4), there is considerable evidence for disturbed hormonal mechanisms infantile spasms. In particular, CSF levels of ACTH have been found to be significantly reduced in groups of infantile spasms patients in a number of studies, and decreased cortisol levels were reported in one study. These findings, as well as the documented efficacy of ACTH and corticosteroid therapy in controlling the seizures in this disorder, are consistent with a role for the hypothalamo-pituitary-adrenal axis in the pathogenesis of infantile spasms. There has been much speculation regarding the mechanisms by which ACTH (and corticosteroids) may exert a beneficial effect (reviewed in Chapter 11, section 2.1.1), including a direct anticonvulsant effect, promotion of brain maturation, and suppression of the immune system.

Baram and her colleagues (Baram et al., 1992a; Baram, 1993; Brunson et al., 2002) have proposed a novel hypothesis for the pathophysiological mechanism of infantile spasms based on primary dysfunction within the brain-adrenal hormonal system. The basic abnormality is postulated to be excessive production of corticotropin-releasing hormone (CRH) during early infancy, as a result of antecedent injury and stress. The elevated CRH levels in turn, at a specific developmental stage with high CRH-receptor abundance, are proposed to induce permanent epileptogenic alterations in brainstem circuits, which would then be the locus of spasm production. The efficacy of ACTH and

corticosteroids would, according to this model, be a result of their known ability to suppress of CRH synthesis. Animal studies (rats) have demonstrated that CRH does have convulsant effects, and that production of seizures is more rapid and potent in infants, as compared to adults (Baram and Schultz, 1991). However, CRH-induced seizures in rats were not prevented by pretreatment with ACTH (Baram and Schultz, 1995), suggesting that ACTH might instead exert its effect by suppressing synthesis and secretion of endogenous CRH. This latter possibility was subsequently confirmed in additional animal studies that demonstrated ACTH activation of melanocortin receptors in the amygdala, with a resultant down-regulation of CRH production (Brunson et al., 2001a,b, 2002).

While this hypothesis is attractive because of its explanatory power, and is supported by considerable evidence from animal studies, its applicability to the production of infantile spasms in humans is still uncertain. The characteristics of CRH-induced ictal behavior and the ictal and interictal EEG patterns are not typical of those seen in infantile spasms. Another difficulty is the absence of elevated CRH levels in the CSF of patients with infantile spasms (Baram et al., 1992a), although, as the investigators suggested, this could simply reflect a non-hypothalamic origin of CRH (i.e., the tissue levels could be elevated, without significantly increased CSF levels). It is also not clear why endogenous ACTH levels would be low in infantile spasms patients, as is observed, in the presence of elevated CRH. But, this presumably could also reflect a confinement of CRH to tissues near the site of abnormal production. Finally, a clinical trial of acutely administered α-helical CRH, a competitive antagonist of CRH, in human infants with infantile spasms did not result in any detectable improvement of the EEG pattern or seizure status (Baram et al., 1999), although, as suggested by the authors, this may reflect a failure of the compound to cross the blood-brain barrier.

4. Animal models

In order to provide a useful tool for research into the causes and treatment of infantile spasms an animal model would need to meet several basic requirements: 1) Be associated with epileptic spasms which have temporal and motor characteristics similar to those present in humans; 2) Persist for a sufficient length of time to permit investigations of the relationship to brain maturation, and to evaluate long-term effects of therapy; 3) Demonstrate a response to ACTH and corticosteroid therapy similar to that observed in humans; and 4) Be associated with alterations of the background EEG pattern that are similar to those present in human infants. At this time no animal model of infantile spasms meeting all of these requirements is available, although several preparations with some similarities to the human disorder have been investigated.

Following the report of Coleman et al. (1971) that 5-OH-tryptophan administration in Down's syndrome was sometimes followed by the onset of

infantile spasms, Klawans et al. (1973) demonstrated that this agent could produce acute seizures in guinea pigs. While these seizures bore some resemblance to those of infantile spasms, sometimes appearing as bilaterally symmetrical and synchronous myoclonic jerks, they were associated with other behavioral events and marked autonomic changes that are not characteristic of infantile spasms. In addition, these seizures were time limited, lasting only a few hours, and, unlike infantile spasms, were blocked by methysergide. However, this model has been useful in studies of serotonin metabolism (e.g., Westheimer and Klawans, 1974), and has provided important information regarding effects of corticosteroids on central serotonergic activity (Nausieda et al., 1982; Pranzatelli and Eng, 1989).

Mares and Velisek (1992) observed that N-methyl-D-aspartate (NMDA), a glutamate receptor agonist, produced an acute seizure disorder in infant rats, which had flexor characteristics, and was age limited, occurring only during the first 3 weeks of life (although tonic-clonic seizures were produced in older animals). Kabova et al. (1996, 1999) evaluated this model in terms of its similarity to infantile spasms, but concluded that it was inadequate. While the seizures bear some resemblance to flexor spasms, and were associated with EEG suppression, no pattern resembling hypsarrhythmia was present interictally, and the seizures did not persist beyond the acute stage. In addition, both pyridoxine and hydrocortisone administration resulted in worsening of the seizures, rather than improvement.

Baram and Schultz (1991, 1995) and Baram et al. (1992b) have evaluated the convulsant effects of corticotropin-releasing hormone (CRH) as a possible model of infantile spasms. The seizures produced in rats by intraventricular CRH administration are characterized by rhythmic chewing and licking (with jaw myoclonus), followed by 'limbic'-type seizures, and occur as a prolonged series. Seizure onset was more rapid in infant rats than in adults, and the threshold was lower. However, the CRH-induced seizures were not prevented by acute or chronic pretreatment of the rats with ACTH. As outlined above (section 3.3), the best available information does not support this as a valid model of infantile spasms.

5. DISCUSSION AND SYNTHESIS

It is clear from consideration of the material reviewed in this chapter that no single pathological feature or neurochemical dysfunction has yet been identified in association with infantile spasms that can be considered to represent a common denominator essential for all cases. On the other hand, groups of infantile spasms patients differ from normal control subjects in a variety of ways, reflecting the widespread disturbance of cerebral function associated with this disorder. The variety of specific structural abnormalities that have been reported in infantile spasms is impressive, both in terms of the locations (cortical, as well as subcortical), and the associated histopathology (neoplastic, atrophic, and

dysplastic). There is an equally diverse group of metabolic disturbances that have been associated with this disorder (Table 10.2), including, among others, various dysfunctions of the metabolic pathways for tryptophan (including the serotonergic system), pyridoxine, catecholamines (including norepinephrine and dopamine), amino acids (including the excitatory neurotransmitters glutamate and aspartate, and the inhibitory amino acid GABA), and neuropeptides (including ACTH). Improved neurodiagnostic imaging techniques, including PET and SPECT, have identified focal metabolic and perfusional abnormalities in many infantile spasms patients, revealing both cortical and subcortical abnormalities often unsuspected by routine CT/MRI studies. Improved and quantitative MRI studies have revealed maturational abnormalities in many patients, including delayed myelination, as well as other morphological changes involving subcortical/brainstem areas. Genetic abnormalities have been identified in numerous instances, including both isolated and familial cases, and it is clear that a variety of loci involving several chromosomes are involved. Finally, there is evidence for disturbed immune system function in many infantile spasms patients.

Several hypothetical models of the pathophysiological process have been proposed, but none can be considered complete, and none, as yet, can explain the diversity of structural and biochemical pathology in a specific manner.

6. FUTURE RESEARCH

The overriding question to be answered is whether infantile spasms has an underlying, unitary, pathophysiological mechanism which is simply triggered by multiple etiological factors, or if it, instead, can result from a variety of disturbances, at least some of which are independent. The former is suggested by the characteristics of the disorder, including the similarity of the ictal events, the interictal EEG patterns and response to ACTH, irrespective of the apparent etiology. The latter is suggested by the failure, so far, to identify any specific abnormality that is present in all patients with this disorder.

In searching for the primary mechanism (or mechanisms) careful consideration should be given to the fact that not all patients with a particular malformation or metabolic dysfunction that has been associated with infantile spasms develop the disorder. For example, infantile spasms is reported to occur in more than half of the patients with hypoxic-ischemic encephalopathy, but it is not possible to predict which patients will be affected and which will not. Similarly, infantile spasms occurs in around half of the patients with tuberous sclerosis, and while subjects with higher numbers of cortical tubers are somewhat more likely to develop the disorder, this is not always true, with some cases occurring in patients with only one lesion, while some subjects with multiple tubers do not develop spasms. Investigation of this phenomenon would be expected to provide crucial information pertinent to the pathophysiological mechanisms. One possible explanation for the observed selective occurrence of

Table 10.2
Biochemical disturbances reported in infantile spasms

Pyridoxine deficiency
Tryptophan metabolism
↓ CSF serotonin
↓ CSF 5-HIAA
↓ CSF kynurenine
↑ CSF 3-OH-kynurenine
↑ CSF kynurenic acid
Catecholamine metabolism
↓ CSF MHPG
↓ CSF tyrosine hydroxylase
Amino acids
↓ CSF GABA
↑ CSF aspartate
↑ CSF homocarnosine
Neuropeptides
↓ CSF ACTH
↑ CSF somatostatin
↓ CSF parvalbumin
↓ CSF methionine enkephalin
↓ CSF cortisol
↓ CSF gangliotetraose-series gangliosides
↑ CSF nitric acid

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infantile spasms among individuals with such similar etiological factors would be the requirement for a second, independent, but concurrent, abnormality. An individual with hypoxic-ischemic encephalopathy, for example, might develop infantile spasms only if a specific genetic abnormality (such as a sporadic chromosomal deletion or translocation) was also present.

It is also evident from the material reviewed above (section 2) that a number of interesting findings reported in the past have not been confirmed, nor have some promising findings been extended. For example, more precise information is needed regarding monoamine metabolism, particularly in view of the central role played by these neurotransmitters in several of the proposed

pathophysiological models. This is especially true for the catecholamines (norepinephrine and dopamine), since reported findings have been variable (section 2.4.2). Similarly, additional studies are needed to clarify the involvement of the immune system in infantile spasms. While several studies have documented abnormalities in groups of patients with this disorder, there are inconsistencies which should be resolved (section 2.7).

Efforts should be accelerated to develop an animal model which demonstrates the major characteristics of infantile spasms. Without such a model, the exact mechanism(s) underlying this disorder will probably remain elusive.

Chapter 11

Treatment

1. BACKGROUND

The primary goals of therapy are control of the spasms and normalization or improvement of developmental status. This chapter is concerned primarily with initial seizure control, while the effects on long-term outcome are considered in Chapter 12. Although the management of many epileptic syndromes is difficult, infantile spasms presents a number of unique problems that have prevented the establishment of widely accepted standard treatment protocols. It is crucial that the physician be fully aware of these problems, and, in particular, be cognizant of their impact upon the interpretation of prior studies of treatment efficacy as well as their influence on determination of optimal response in individual cases.

1.1 Spontaneous remission

It has long been recognized that infantile spasms is an age-dependent disorder, and that, regardless of treatment, spasms eventually cease in the majority of patients. For example, Jeavons et al. (1973) reported that by the age of 1 year 28% of children were free of spasms, and almost all (92%) were spasm free by age 7, whether or not they had responded to medical therapy. We conducted a retrospective study of this phenomenon (Hrachovy et al. 1991) by examining the records of 44 children with infantile spasms who had been treated prior to 1960 with either phenytoin or metharbital, drugs which currently are believed to have no effect in this disorder. In this group, spontaneous remission was observed as early as one month after spasm onset, and by one year spasms had ceased and the hypsarrhythmic EEG pattern had disappeared in 25% of the patients. While placebo studies have been rare in this disorder because of ethical concerns over withholding therapy, a recent very short-term (5 days) comparison of vigabatrin and placebo reported a 10% initial response (2 of 20 patients) to

the placebo. Finally, there have been a number of individual case reports documenting spontaneous remission of spasms (Bachman, 1981; Nalin et al., 1985; Hattori, 2001). Fig. 11.1 demonstrates this phenomenon in a patient whose spasms ceased prior to institution of therapy (Hrachovy and Frost, 2001). Consequently, it is clear that the spontaneous remission rate should be carefully considered when assessing the apparent response to any therapeutic modality, particularly in the case of noncomparative studies and studies evaluating duration of treatment.

1.2 Difficulty in documenting therapeutic response

As discussed in Chapter 4, the ictal events associated with this disorder are often very brief, and, in addition, may be quite subtle. If the child is not being directly observed at the time of the event, it is certain that the spasm will not be recognized and documented, while even if the event is observed it is often impossible to conclusively identify it as an epileptic spasm. This presents a major problem for the determination of an initial response to therapy if the efficacy measure is based upon such subjective reports of parents or other observers, as has most often been the case in reported therapeutic trials. While an objective technique — EEG/video monitoring — exists for more precisely determining seizure frequency over adequate time periods (Chapter 5), this method has been used only rarely, and for a limited number of therapeutic modalities. The failure to use objective methods undoubtedly has contributed significantly to the marked differences in response rates reported by various investigators evaluating the same treatment. We have shown previously (Hrachovy et al., 1979; Kellaway et al., 1979; Hrachovy and Frost, 2001) that parents often underestimate spasm frequency to a significant degree in comparison to the results of 24-hour EEG/video monitoring. For example, in one study of hormonal therapy parents reported a complete cessation of spasms in 8 of 24 patients. Monitoring of these same patients revealed that 3 of the 8 patients (38%) thought to be controlled were in fact continuing to have spasms. While less common, we have also observed the converse of this, with parents reporting that spasms continued to occur, when monitoring revealed no events of epileptic character (Fig. 11.2). This problem has been compounded by the fact that highly variable consideration has been given to the proper training of parents and others involved in documenting spasm frequency when this method is used. In some instances, parents were specifically trained to recognize spasms, while excluding normal events, and some studies included a definite daily schedule of intensive observation times. In the majority of studies, however, little or no mention of the exact method is given, and it is assumed that observation in these instances was probably sporadic and less reliable.

Also contributing to the difficulty in establishing clear-cut efficacy measures has been the widespread use of a graded response measure when reporting the

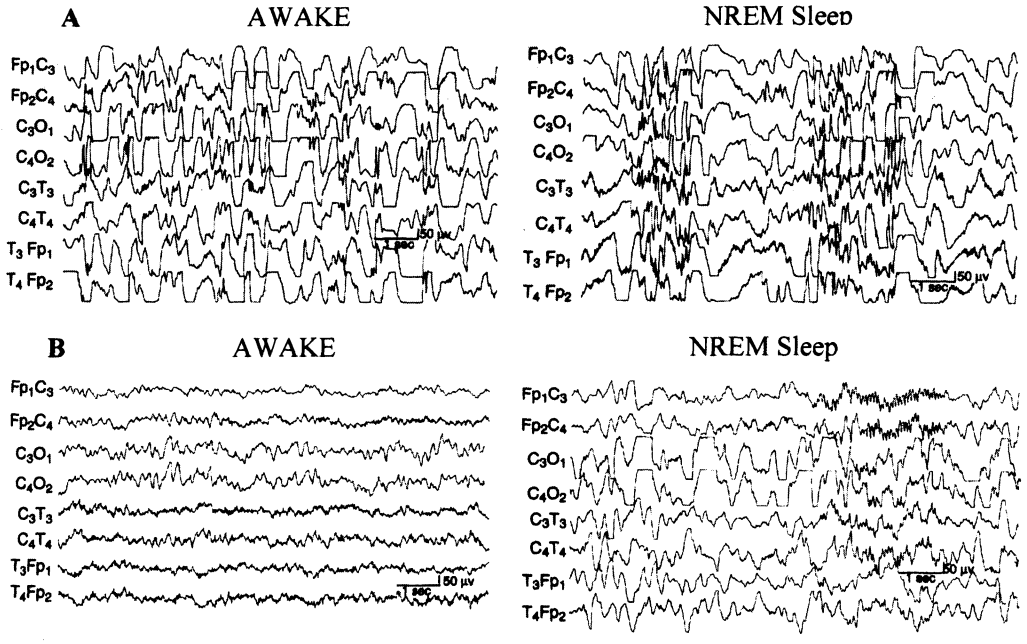

Figure 11.1 Spontaneous remission in a 7-month child with cryptogenic infantile spasms who was not treated due to an infection. Selected samples of the awake and sleep EEG tracings are illustrated. A. Baseline recording shows hypsarrhythmia, and spasms occurred during the study. B. A repeat recording made 3 weeks later shows normal activity both awake and asleep, and no spasms occurred during the 24-hour session. (Reprinted from, Pediatric Epilepsy Diagnosis and Therapy, Pellock, J. M., Dodson, W. E., and Bourgeois, B. F. D., Eds. Severe encephalopathic epilepsy in infants: West syndrome. Hrachovy, R. A. and Frost, J. D., Jr. Figure 13-1, page 181. Copyright 2001; with permission of Demos Medical Publishing)

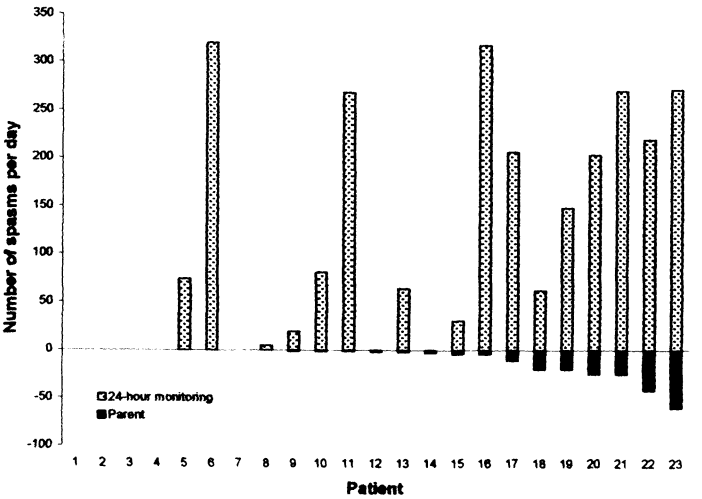

Figure 11.2 Comparison of parental estimate of spasm frequency and the results of 24-hour EEG-Video monitoring. The coefficient of determination (r^2) between the two counts was 0.26.

results of clinical trials. There is no convincing evidence that spasm frequency ever decreases in a graded manner when a particular therapeutic agent is effective. Furthermore, monitoring studies have shown that there is a marked fluctuation in spasm frequency over time (Fig. 11.3; Hrachovy and Frost, 1986). Such variation in spasm occurrence basically renders a graded response approach useless. When objective measures have been used to document spasm frequency (Hrachovy et al., 1979, 1981, 1983) a graded response has not been observed, and the response is all-or-none – there is either complete control, with cessation of spasms, or no control. This point is also emphasized in the current Guidelines for Antiepileptic Drug Trials in Children (Commission, 1994), which states with respect to West syndrome "A decrease of 50% in seizure frequency is clinically irrelevant. Complete cessation of spasms is therefore the main objective of treatment". Thus, the common practice of designating as responders patients who show a 50 % or greater decrease in spasm frequency after treatment, in comparison to the baseline value, tends to artificially inflate the efficacy measure since such studies almost never counterbalance this contribution by subtracting the number of patients who have an actual increase of spasm frequency. Thus, random fluctuations in spasm frequency (which are known to be common in this disorder) artificially bias the result in favor of the treatment.

Finally, the above methodological problems inherent in the majority of published clinical trials are further compounded by the fact that most studies have been uncontrolled, unblinded, and retrospective. The influence of these three elements is more difficult to quantify, but they clearly increase the chance

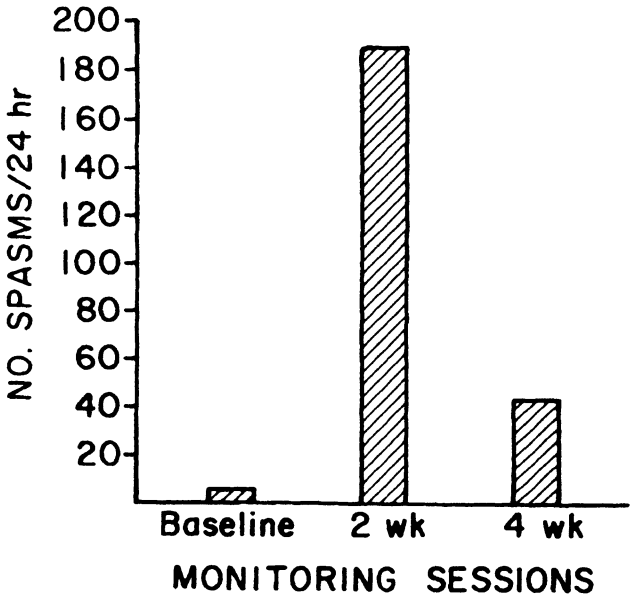

Figure 11.3 Variation of spasm frequency in a patient monitored at 2-week intervals. (Reprinted from *Intractable Epilepsy*, Schmidt, D. and Morselli, P. L., Eds. Hrachovy, R. A. and Frost, J. D., Jr. Intensive monitoring of infantile spasms. Pages 87-97, copyright 1986, with permission from Lippincott Williams & Wilkins)

that results may be influenced by unsuspected factors, and so reduce the overall consistency of the studies as a group.

The extent of these methodological issues is documented in Table 11.1, which shows the number of treatment trials between 1958 and 2002 that fell into various experimental design categories for several of the most commonly prescribed therapeutic modalities. The response rate ranges shown here are based only on those studies in which it was possible to express the efficacy in terms of the percentage of subjects showing a complete cessation of spasms within the evaluation period (although trials providing only a graded measure of spasm frequency are included in the total number of studies). In addition, we have only included treatment categories in which more than 2 therapeutic trials have been reported for that modality. A listing of the studies included in Table 11.1, organized by treatment type, is provided in Appendix 2.

Studies incorporating the most rigorous design parameters (i.e., prospective design, randomization of patients at entry, blinded protocol, and use of objective methods for assessing response to therapy) are listed in the first column of Table 11.1, while studies with progressively less stringent requirements are shown in columns 2 through 6 (column 6 also includes all studies with fewer than 11

Table 11.1* Summary of 214 therapeutic trials (1958 – 2002)

Therapy	*Type of Trial*					
	24h Mon. Pros. Rand. Blinded	**Subj. Pros. Rand. Blinded**	**24h Mon. Pros. Open**	**Subj. Pros. Open**	**Retro.**	**Case reports**
ACTH	n =3 42-58 %		n = 1 74 %	n = 11 20-94 %	n = 27 7-93 %	n = 25 0-100 %
ACTH (High dose)	n = 2 50-87 %			n = 1 93 %	n = 4 54-100 %	n = 6 50-100 %
Corticosteroid	n = 2 29-33 %		n = 1 25 %	n = 3 33- 67 %	n = 9 14-77 %	n = 9 0-100 %
Vigabatrin		n = 1 35 %	n = 1 48 %	n = 13 23-100 %	n = 7 47-100 %	n = 8 0-100 %
Nitrazepam	n = 1			n = 2 25 %	n = 5 20- 82 %	n = 3 0-30 %
Valproate		n = 1		n = 2 22-50 %	n = 4 18-43 %	n = 5 0-50 %
Pyridoxine (vitamin B_6)				n = 5 3-29 %	n = 3 0-27 %	n = 4 0-100 %
Surgery				n = 1 61 %		n = 16 0 – 100 %
Clonazepam				n = 2 12 %	n = 2 25-26 %	n = 5 0-40 %
Immunoglobulin				n = 2 26-82 %		n = 4 33-43 %
TRH				n = 2 47-54 %	n = 1 31 %	n = 1
Zonisamide				n = 3 20-36 %	n = 2 38 %	n = 2 33 %
Topiramate			n = 1 45 %	n = 2 33-50 %	n = 1 15 %	n = 2 20-57%
Lamotrigine				n = 4 15-29 %		n = 1 100%
Felbamate				n = 1		n = 2 75 %

24h Mon. = 24-hour EEG/Video monitoring; Subj. = Subjective observation by parent/caregiver and/or short-term EEG/Video monitoring (< 24 hours); Pros. = Prospective design; Rand. = Randomized study; Open = Open label design; Retro. = Retrospective design; Case reports = Case reports or trials with fewer than 11 subjects

n = number of trials in category
Range of reported initial response to therapy is expressed as the percentage of patients exhibiting complete cessation of spasms.

* A listing of the studies included in this table is provided in Appendix 2.

subjects). It is clear from inspection of this table that most therapeutic trials in this disorder have not used rigorous techniques. For example, of the 214 studies reviewed, only 10 (5%) were prospective with randomized and blinded protocols (columns 1 and 2). Only 12 studies (6%) made use of objective 24-hour EEG/Video monitoring techniques to evaluate the response to therapy (columns 1 and 3), with the vast majority relying on subjective parental/caregiver observations. Overall, 69% of the studies were either retrospective or fell into the case report category (columns 5 and 6). Of the 15 major therapeutic agents included in this table, 8 (53%) have never been evaluated with either a prospective/randomized/blinded design, or with use of objective 24-hour EEG/video monitoring. Consequently, as discussed below in the sections describing specific treatment modalities, it is usually not possible to resolve the sometimes marked differences in response rates reported by various investigators.

2. MEDICAL THERAPY

2.1 ACTH and Corticosteroids

In 1958, Sorel and Dusaucy-Bauloye reported the effectiveness of ACTH in stopping the spasms and improving the EEG in a small number of patients with infantile spasms. Soon after this report, Low (1958) reported similar beneficial effects with corticosteroid treatment. Over the past half-century, numerous confirmatory studies have appeared in the world literature (Table 11.1). However, because most of these studies have been plagued with methodological shortcomings (see above), controversies abound concerning which therapeutic agent if any, is more effective and which specific treatment regimens (i.e., high vs. low dose, short duration vs. long duration) should be used.

2.1.1 Mechanism of Action

At the current time no animal model of infantile spasms exists, and, thus, the mechanism(s) by which ACTH and corticosteroids exert their antiepileptic effects is (are) totally speculative. Although certain traditional anticonvulsants may stop spasms in some patients (see below), certain characteristics of the response to hormonal therapy, i.e., only short courses of hormonal therapy (less than 2 weeks) are required in most cases to produce a permanent response, suggest that the mechanism by which ACTH and corticosteroids produce their antiepileptic effect is unlike that of traditional anticonvulsants.

In addition, one important controversial question remains to be answered: Does ACTH work directly on the brain to produce its antiepileptic action, or is its effect related to corticosteroids which are released by ACTH stimulation of the adrenal cortex? Certain observations suggest that ACTH may produce its antiepileptic effect independent of corticosteroid activity. It has been reported

that ACTH may stop spasms in patients whose adrenal function is suppressed (Crosley et al., 1980; Farwell et al., 1984). Also, the observation that ACTH may stop the spasms and improve the EEG in patients who fail to respond to corticosteroid therapy, and vice versa, lends some support to this hypothesis. Attempts to further address this controversy by using ACTH fragments devoid of adrenocortical stimulatory effect have been unsuccessful (Pentella et al., 1982; Willig and Lagenstein, 1982 [ACTH 4-10]; personal observations, ACTH 4-9.)

Direct Anticonvulsant Effects It has been proposed that ACTH and corticosteroids may have direct anticonvulsant effects. In animal models, corticosteroids have been reported to reduce hippocampal excitability in vitro (Vidal et al., 1986), while ACTH has been shown to have both anticonvulsant and proconvulsant activity. In adult rats, ACTH increases the threshold for electroshock seizures, and higher doses of ACTH delay kindling (Pranzatelli, 1994). Conversely, in immature rats, ACTH has been demonstrated to have a proconvulsant effect characterized by a reduction of the threshold for minimal clonic electroshock seizures (Pranzatelli, 1994).

Inhibition of CRH It has been hypothesized that stress-induced increase of corticotropin-releasing hormone (CRH) results in infantile spasms, and that ACTH may exert its anticonvulsant effect through inhibition of this compound (Baram, 1993; Baram and Hatalski, 1998). In infant rats, CRH has been shown to be a potent convulsant (Baram and Schultz, 1991; Baram et al., 1992b; see also Chapter 10). It is suggested that ACTH eliminates infantile spasms by suppressing the age-specific, endogenous, convulsant effect of CRH. To test the hypothesis, α-helical CRH, a competitive antagonist of CRH, was used to treat 6 infants with infantile spasms (Baram et al., 1999). However, since no beneficial effect of this peptide, in terms of EEG changes or seizure control, was demonstrated, the authors concluded that peptide analogs of CRH do not cross the blood brain barrier and that nonpeptide compounds with greater permeability will be required to test this hypothesis adequately.

Promotion of Brain Maturation and Growth ACTH accelerates myelination and dendritic sprouting and stimulates RNA and DNA synthesis (Palo and Savolainen, 1974; Ardeleanu and Sterescu, 1978; Pranzatelli, 1994) Steroids and ACTH stimulate growth of neuroblasts in culture (Riikonen, 1983; Pranzatelli, 1994) and induce various enzymes of the central nervous system, e.g., (Na^+/K^+) ATPase in the developing cortex of kittens (Huttenlocher and Amemiya, 1978). The modulation of such physiologic events in the immature brain is one of the long standing and frequently proposed hypotheses concerning the mode of action of ACTH and steroids in infantile spasms (Riikonen, 1983).

Modulation of Neurotransmitter Systems ACTH and corticosteroids may modulate various neurotransmitter systems in the central nervous system. Dysfunction of certain neurotransmitter systems, particularly serotonergic and adrenergic, has been suggested as the pathophysiological mechanism underlying infantile spasms (Hrachovy and Frost, 1989a; see chapter 10). Corticosteroids have been shown to block tryptophan-induced myoclonus (Klawans et al., 1973)

and to increase GABA activity in rat brain (Kendall et al., 1982). ACTH has been reported to reduce serotonin 5-HT_2 sites in cortex, increase B-adrenergic receptor binding in cortex, and increase or decrease GABA and dopamine D_2 receptor sites (Dunn and Gispen, 1977; Pranzatelli, 1994). The effects of ACTH on metabolism of neurotransmitters have been variable and are often age dependent. For example, in developing animals, ACTH treatment did not alter whole brain levels of 5-hydroxytryptamine, 5-hydroxyindolacetic acid, dopamine, dihydroxyphenylacetic acid, homovanillic acid, or glutamic acid decarboxylase (Ito et al., 1985), whereas in adult animals, the effects of ACTH on CNS levels of dopamine, norepinephrine, acetylcholine, serotonin and GABA have included increased synthesis and turnover (Pranzatelli, 1994).

In infantile spasm patients, the effects of hormonal therapy on various neurotransmitter metabolite levels have been inconclusive (Hrachovy and Frost, 1989a). Also, treatment of infantile spasm patients with antiserotonergic and antiadrenergic drugs has not been very successful (Hrachovy et al., 1988b, 1989; see Section 2.3.4, below). Therefore, the significance, if any, of the neuromodulatory effects on various neurotransmitter systems by ACTH and cortiosteroids in relation to infantile spasms is not clear.

Suppression of the Immune System The hypothesis that infantile spasms may result from an immunologic defect has been discussed in chapter 10. The observation that very brief courses of ACTH or cortiosteroids is usually all that is required to control spasms in many patients makes this hypothesis very attractive. However, a direct link between infantile spasms and dysfunction of the immune system has not been established.

2.1.2 Hormonal Preparations Used

Different formulations of ACTH are utilized throughout the world to treat infantile spasm patients. In the United States, a natural gel preparation of ACTH is used, whereas, in Japan and many other countries, synthetic preparations are used. The potency of the gel preparation in the United States is measured in units, whereas, the synthetic preparations are measured in milligrams. One milligram of synthetic ACTH is considered to be equivalent to 40 units.

A variety of corticosteroid preparations have been used to treat infantile spasm patients. These include prednisone, hydrocortisone, cortisone, prednisolone and dexamethasone. The most commonly used agent has been prednisone.

2.1.3 Therapeutic Approaches

Over the past four plus decades, several therapeutic approaches utilizing ACTH and corticosteroids have evolved in the treatment of infantile spasms. These include the following:

ACTH monotherapy ACTH is generally recognized as the "gold standard" for the treatment of this disorder. However, there continues to be considerable controversy concerning the dosage of ACTH that should be used and the duration of treatment utilized to attain the best seizure control. Two basic approaches are currently used. Some investigators use relatively higher doses of ACTH (40-160 u/day) at the beginning of treatment, and then taper the dose of ACTH over a relatively long (3-12 months) duration (Chevrie and Aicardi, 1971; Snead et al., 1983, 1989; Lombroso, 1983; Koo et al., 1993; Baram et al., 1996; Cossette et al., 1999). Others utilize lower doses (< 1-40 u/day) for shorter periods of time (generally 2-8 wks) (Sorel, 1959; Trojaberg and Plum, 1960; Jeavons and Bower, 1964; Harris, 1964; Willoughby et al., 1966; Hrachovy et al., 1980, 1983, 1994b; Riikonen, 1982; Miyazaki et al., 1992; Maeda et al., 1997; Yamamoto et al., 1998). However, independent of the therapeutic approach used, most investigators report that if ACTH is effective, the response is usually seen within one to two weeks of initiation of treatment. As summarized in Table 11.1, the response rates for the two therapeutic approaches are highly variable. This fact is probably related to the subjective method of determining spasm frequency (parental observation) used in most studies. Some of the most favorable results have been reported by Snead et al. (1983, 1989) utilizing high-dose long-duration ACTH therapy (beginning dosage 150u/m^2/day, tapered over 3 mos.) In one study of 30 patients studied retrospectively (Snead et al., 1983), it was reported that 100% of the patients experienced cessation of spasms following high-dose ACTH therapy, and that in 29 of these patients the EEGs returned to normal. In a subsequent uncontrolled, non-randomized and non-blinded study (Snead et al., 1989) 14 of 15 (93%) patients treated with high-dose ACTH experienced cessation of spasms and reversion of the EEG to normal.

Several other investigators (Hashimoto et al., 1981; Satoh et al., 1982; Ohtsuka et al., 1983; Haga et al., 1992; Kuriyama et al., 1992; Yanagaki et al., 1999; Kohyama et al., 2000), in non-controlled, non-blinded, open trials in small patient groups, have reported very high response rates with low-dose ACTH. However, the majority of non-controlled, non-blinded, retrospective or prospective studies report response rates between 40-80% for either high-dose or low-dose ACTH (Sorel and Dusaucy-Bauloye, 1958; Dobbs and Baird, 1960; Jeavons and Bower, 1964; Harris, 1964; Fukazawa, 1972; Sakuma et al., 1980; Riikonen, 1982; Lombroso, 1983; Riikonen and Perheentupa, 1986; Riikonen et al., 1989; Riikonen and Simell, 1990; Ito et al., 1990, 2002; Koo et al., 1993; Sher and Sheikh, 1993; Heiskala et al., 1996; Vigevano and Cilio 1997; Antoniuk et al., 2000).

Three prospective, controlled, blinded trials of high-dose or low-dose ACTH in which video/EEG monitoring was used to determine objective response rates have also yielded conflicting results. In one study of high-dose ACTH (150u/m^2/day) vs. prednisone by Baram and colleagues (1996), 13 of 15 (87%) patients treated with high dose ACTH responded. In another study in which

low dose ACTH (20-30u/day) was compared with prednisone therapy (Hrachovy et al., 1983), five of 12 patients (42%) treated with low dose ACTH responded. In a third controlled study (Hrachovy et al., 1994b), only 13 of 26 (50%) of patients receiving the same dosage (150u/m^2/day) of ACTH as in the Baram study became seizure-free. In this same blinded comparative trial of high-dose vs. low-dose ACTH, 14 of 24 (58%) of patients treated with low dose ACTH (20-30 units/day) responded. Unfortunately, the number of patients in these controlled, blinded, objectively evaluated, studies is too small to reach meaningful conclusions.

Corticosteroid monotherapy As mentioned above, prednisone is the corticosteroid most commonly used to treat infantile spasms. Dosages of prednisone employed have varied from 1-15 mg/kg /day and duration of therapy has ranged from 2 wks- 32 wks. As summarized in Table 11.1, response rates similar to those seen with low-dose or high-dose ACTH therapy have been reported with corticosteroids. In the larger retrospective series, the response rates have varied from 38-77% (Crowther, 1964; Danielsen, 1965; Klein, 1970; Fukazawa, 1972; Lombroso, 1983; Snead et al., 1983; Hancock and Osborne, 1998). Two prospective, blinded, controlled studies utilizing video/EEG monitoring to determine response comparing prednisone to ACTH therapy have been performed. In one study mentioned above, (Hrachovy et al., 1983), 4 of 12 (33%) patients treated with prednisone (2 mg/kg/day) responded compared to 5/12 (42%) patients treated with ACTH (20-30u/day). In the other study, also mentioned above, (Baram et al., 1996), 4 of 14 (29%) patients treated with prednisone (2 mg/kg/day) responded compared to 13/15 (87%) of patients treated with high dose ACTH (150u/m^2/day). Again, the numbers of patients in these two studies are too small to reach meaningful conclusions.

ACTH followed by corticosteroid monotherapy The general scheme in this approach is to use ACTH (either high- or low-dose) for several weeks and then replace ACTH with corticosteroids for weeks to months. No additional benefit has been demonstrated with this approach (Oftedal, 1967; Lerman and Kivity, 1982; Lombroso, 1983).

ACTH and other agents given simultaneously ACTH has been used simultaneously with various agents, most commonly valproic acid (Siemes et al., 1988; Nolte, et al., 1988), vitamin B_6 (Seki, 1990; Takuma, 1998; Hirai et al., 1998)), nitrazepam (Feng et al., 1991), corticosteroids (Low, 1958; Millichap et al., 1962; Oftedal, 1967; Riikonen, 1982; Farwell et al., 1984), clonazepam (Nolte et al., 1988) . Response rates using such combined therapy were usually similar to those of ACTH used alone.

2.1.4 Relapse Rates

Comparison of relapse rates between studies is difficult because of differences in study design and the fact that most studies relied on parental observation to determine spasm frequency. The relapse rate ranges reported for

high dose ACTH are 13-59% (Snead et al., 1983, 1989; Koo et al., 1993; Hrachovy et al., 1994b; Baram et al., 1996; Cossette et al, 1999), those for low dose ACTH are 21-100% (Sorel, 1959; Jeavons and Bower, 1964; Harris, 1964; Haga et al., 1992; Miyazaki et al., 1992; Hrachovy et al., 1994b; Maeda et al., 1997; Yamamoto et al., 1998; Yanagaki et al., 1999) and those for corticosteroids are 9-100% (Pauli et al., 1960; Jeavons and Bower, 1964; Danielsen, 1965; Klein, 1970; Snead et al., 1983). The relapse rates for the majority of studies in all treatment groups generally range from one quarter to one third of patients.

2.1.5 Observations Utilizing Video/EEG Monitoring

The major observations concerning therapeutic response to ACTH and/or prednisone seen in our own controlled prospective studies (Hrachovy et al., 1979, 1980, 1983, 1994b) utilizing video EEG monitoring to document response are: **1)** Response to therapy is all or none, **2)** Only a short course of hormonal therapy (< 2 wks) is required in most patients to obtain a response. **3)** After a response to hormonal therapy is documented, the therapy can be discontinued immediately and the response maintained. **4)** ACTH failures may respond to prednisone and vice versa. **5)** If a relapse occurs, a second course of hormonal therapy is usually effective. **6)** Disappearance of the hypsarrhythmic EEG pattern may occur in patients who continue to have spasms following hormonal therapy. This latter point is very important because many physicians rely heavily on the routine EEG to help determine if a response has occurred. **7)** Relatively few patients will exhibit a normal EEG at the time a response is documented (Table 11.2).

2.1.6 Predictors of Response

Two factors which have been reported to be associated with a good response (cessation of spasms) to hormonal therapy are treatment lag and whether a patient is classified as cryptogenic or symptomatic. Several authors (Trojaberg and Plum, 1960; Oftedal, 1967; Sakuma et al., 1980; Lerman and Kivity, 1982; Riikonen, 1983; Sher, 1993) have reported better response rates in patients with short treatment lags (usually < 1month). However, this finding has not been observed by others (Willoughby et al., 1966; Pache and Troger, 1967; Hrachovy et al., 1979, 1980, 1983, 1994b; Fois et al., 1987; Koo et al., 1993; Holden et al., 1997; Young, 2001). In many studies, cryptogenic patients have been reported to respond better to hormonal therapy than symptomatic patients (Trojaberg and Plum, 1960; Oftedal, 1967; Sakuma et al., 1980; Lerman and Kivity, 1982; Lombroso, 1983; Riikonen and Perheentupa, 1986; Sher et al., 1993); however, this finding is not universally observed (Willoughby et al., 1966; Pache and Troger, 1967; Hrachovy et al., 1979, 1980, 1983; Fois et al., 1987; Koo et al., 1993; Holden et al., 1997; Young, 2001).

Table 11.2
EEG findings in 53 patients at time of documented cessation of spasms

EEG Findings	*Percentage of Patients*
Hypsarrhythmia	**0**
Normal	**9**
Normal background activity	**32**
Sharp- or spike-and-slow-wave foci	30
In temporal region only	15
In temporal and other regions	15
Focal slow activity only in temporal region	4
Intermittent rhythmic bifrontal sharp-and-slow-wave activity	4
Unilateral suppression of background activity	6
High-voltage fast activity	8
Abnormally slow and disorganized background activity	**59**
Alpha rhythm present	21
Sharp- or spike-and-slow-wave foci	49
In temporal region only	15
In temporal and other regions	30
In other regions only	4
No foci	2
Intermittent rhythmic bifrontal sharp-and-slow-wave activity	11
Intermittent rhythmic bifrontal delta activity	19
Intermittent rhythmic bi-occipital delta activity	8
Unilateral suppression of background activity	8

Rating et al. (1987) devised a scoring system for assessment of the interictal EEG, in which points were accumulated for certain electrographic features, including hypsarrhythmia (10 points), absence of sleep patterns (10 points), focal and generalized epileptic discharges (5 points each), and slow wave foci (5 points). They found that higher scores (>40) were associated with patients who subsequently did not respond to ACTH treatment, or who relapsed following an initially favorable response.

2.1.7 Side Effects

ACTH and corticosteroid administration in infantile spasms is often associated with side effects, the most common of which are listed in table 11.3, and summarized below.

Cardiovascular Hypertension is one of the most common side effects of hormonal therapy in infantile spasm patients and is reported in almost all studies in which side effects are mentioned. Evidence suggests that hypertension occurs

Table 11.3
Side effects reported in patients with infantile spasms treated with ACTH or corticosteroids

Cardiovascular
*Hypertension
*Hypertrophic cardiomyopathy
Brain
*Brain shrinkage
Subdural Effusion
Subdural hematoma
Intracranial hemorrhage
Immunosuppression
*Infection of various organ systems
Gastrointestinal
Ulceration
Hemorrhage
Genitourinary
Nephrocalcinosis
Electrolyte abnormality
Hypokalemia
Musculoskeletal
Osteoporosis
Other
*Irritability and behavioral disturbances
*Cushingoid features and weight gain
*Acne and hirsutism

*Common

more commonly in patients treated with higher doses (Riikonen and Donner, 1980; Hrachovy et al., 1983, 1994b).

Hypertrophic cardiomyopathy, diagnosed by echocardiographic studies, has been reported to develop in 78-90% of patients treated with ACTH (Lang et al., 1984; Alpert, 1984; Kupferschmid and Lang, 1987; Redel and Herding, 1987; Bobele et al., 1993; Riikonen, 1993; Starc et al., 1994). This condition is reversible within months of stopping ACTH therapy. Possible explanations for this condition include: thickening of the myocardium secondary to interstitial edema caused by increased sodium and water content, thickening of the myocardium secondary to arterial hypertension, hyperinsulinism (a condition that causes cardiac hypertrophy in infants of diabetic mothers), and a direct effect of ACTH on myocardial cells (Lang et al., 1984; Kupferschmid and Lang, 1987).

Immune System Infection of various organ systems has been reported to occur in infantile spasm patients including pulmonary, circulatory, genitourinary, gastrointestinal, ear, central nervous system and skin (Danielsen, 1965; Riikonen and Donner, 1980; Lerman and Kivity, 1982; Lombroso, 1983; Colleselli et al., 1986; Riikonen and Simell, 1990; Haga et al., 1992; Shamir et al., 1993; Kusse et al., 1993; Hrachovy et al., 1994b). Pneumonia is one of the most commonly occurring infections and may result in death. Therefore, development or pre-existence of a pulmonary or other serious infection is cause to delay or discontinue ACTH or corticosteroid therapy.

Brain Computed tomography and MRI studies have shown that brain shrinkage may develop in many patients treated with ACTH or corticosteroids. This phenomenon occurs in patients treated with either low or high doses (Lagenstein et al., 1979a,b; Maekawa et al., 1980; Okuno et al., 1980; Siemes et al., 1981; Hara et al., 1981; Carollo et al., 1982; Satoh et al, 1982; Klepel et al., 1983; Ito et al., 1983; Hrachovy et al., 1983; Glaze et al., 1986; Ludwig, 1987; Howitz et al., 1990; Konishi et al, 1992; Heiskala et al., 1996; Yanagaki et al., 1999) and reportedly reverses after discontinuation of hormonal therapy. However, in several studies (Okuno et al., 1980; Ito et al, 1983; Glaze et al., 1986; Mahdi et al., 1990) the apparent brain shrinkage was not reversible in 12-44% of patients. Several explanations have been suggested for these changes seen during hormonal therapy including communicating hydrocephalus, loss of water, alterations in blood brain barrier and inhibition of brain growth (Lagenstein, 1979b; Lyen et al., 1979; Hara et al., 1981; Siemes et al., 1981; Carollo et al., 1982; Glaze et al., 1986; Maeda et al., 1997).

Subdural hematoma or subdural effusion has been reported to occur rarely in infantile spasm patients treated with hormonal therapy (Okuno et al, 1980; Hara et al., 1981; Satoh et al., 1982; Ito et al., 1983, 2000). Also, intracerebral hemorrhage, probably secondary to hypertension has been rarely reported (Riikonen and Donner, 1980).

Gastrointestinal Ulceration and/or hemorrhage within the gastrointestinal tract have been reported rarely in infantile spasm patients receiving ACTH or corticosteroid (Myles and Daly, 1974; Dreifus et al., 1986; Glauser and Rogers, 1990).

Genitourinary Nephrocalcinosis has been reported to occur in some infants receiving ACTH and corticosteroids. This complication was identified by imaging studies (Rausch et al., 1984) and at autopsy (Riikonen et al., 1986), although in small numbers of patients.

Electrolyte abnormalities The most common electrolyte disturbance reported in infantile spasm patients treated with ACTH or corticosteroids is hypokalemia (Lombroso, 1983; Lang et al., 1984; Riikonen et al., 1986; Riikonen and Simell, 1990; Haga et al., 1992; Hrachovy et al, 1994b). This condition usually occurs in patients receiving higher doses and longer durations of hormonal therapy (Lombroso, 1983; Hrachovy et al., 1994b).

Skeletal On rare occasions, osteoporosis has been reported to occur in infantile spasm patients treated with ACTH and corticosteroids (Riikonen and Donner 1980; Lombroso, 1983; Riikonen et al., 1986). This side effect would not be expected unless patients are receiving prolonged courses of hormonal therapy.

Behavioral Irritability and other behavioral changes, including sleep disturbances, have been reported to occur in 33-85% of patients with infantile spasms treated with ACTH or corticosteroids (Riikonen and Donner, 1980; Lombroso, 1983; Snead et al., 1983, 1989; Driefuss et al., 1986; Hrachovy et al., 1994b; Chiron et al., 1997; Vigevano and Cilio, 1997; Hancock and Osborne,

1998; Cossette et al., 1999). These effects are transient and rapidly subside when hormonal therapy is discontinued.

Cushingoid features Many patients treated with ACTH or corticosteroids will develop significant weight gain and exhibit cushingoid features. These changes are often dose-related, being more pronounced in patients receiving higher doses (Danielsen, 1965; Riikonen and Donner, 1980; Lerman and Kivity, 1982; Lombroso, 1983; Snead et al., 1983, 1989; Lang et al., 1984; Driefuss et al., 1986; Hrachovy et al., 1994b; Chiron et al., 1997; Cossette et al., 1999).

Skin Acne and hirsutism may develop in infants treated with ACTH or corticosteroids (Riikonen and Donner, 1980; Snead, 1983; Lombroso, 1983); however, these are relatively minor effects and disappear rapidly with discontinuation of therapy.

2.2 Anticonvulsants

2.2.1 Benzodiazepines

The benzodiazepines constitute a large group of structural analogs which have multiple physiological effects. In addition to anticonvulsant properties, these agents also demonstrate sedative/hypnotic and anxiolytic effects, and consequently have been widely used in clinical medicine. While the mechanisms by which the benzodiazepines produce their alterations of brain function are still incompletely understood, it is clear that they have specific binding sites within the central nervous system. Considerable evidence exists that the major effect is exerted upon the GABA (γ-aminobutyric acid) receptor complex which comprises a chloride channel found on most cortical neurons, and which, when activated synaptically by GABA, results in membrane hyperpolarization and inhibition of neuronal activity. Benzodiazepine binding to the receptor appears to potentiate the effect of GABA, and thus increases the overall inhibitory effect (Ko et al., 1997). Because of the demonstrated anticonvulsant effect of these compounds, several benzodiazepines have been evaluated for efficacy in infantile spasms.

Clonazepam Several studies of the effectiveness of clonazepam in infantile spasms were reported between 1972 and 1988, and the results do not suggest a high degree of efficacy. In the only prospective study that reported the number of subjects achieving complete cessation of spasms (Martin and Hirt, 1973), the response rate was only 12% in a group of 17 patients receiving 3-4 mg/day. A larger, retrospective, study of 42 patients (Dummermuth and Kovacs, 1973) determined a 26% response rate. Another prospective study of 24 patients (Vassella et al., 1973) reported a response rate of 21%, based upon a >50% decrease of spasm frequency, using a clonazepam dose of 0.1-0.3 mg/kg/day. In several smaller trials (5 to 12 subjects), the reported response rates ranged between 0% and 40% for spasm cessation (Hanson and Menkes, 1972; Carson and Gilden, 1975; Sakuma et al., 1980; Nolte et al., 1988). Finally, in a study

which evaluated the response to clonazepam (0.03-0.18 mg/kg/day for 8 weeks) in a group of 8 patients that had failed to respond to either ACTH (20-30 units/day for 8 weeks) or prednisone (2 mg/kg/day for 8 weeks), there were no responders (Hrachovy et al., 1983).

Based upon the available evidence, it is not possible to conclude that clonazepam has a significant degree of efficacy in this disorder. The response rates reported in the majority of these studies (0-25%) are low, and the possibility that most, or even all, of the apparent successes were a result of spontaneous remission can not be excluded.

Minor side effects of clonazepam therapy such as drowsiness, hypotonia, increased salivation, difficulty swallowing, and other feeding difficulties were relatively common in the reported studies, but more severe problems were rare (hyperexcitability, confusional state). There was one reported death due to aspiration pneumonia.

Nitrazepam has been used as a therapy for infantile spasms for more than 30 years, and during this time a number of studies of its efficacy have been conducted. While the results have been quite variable, at least some degree of effectiveness is suggested by the results of these trials. In a controlled, blinded, and randomized comparative study (Dreifuss et al. 1986) there was no significant difference in the initial response (>50% decrease of seizure frequency) to nitrazepam (67%) and ACTH (57%). Unfortunately, these investigators reported the response rate only in terms of a graded decrease of spasm frequency after 4 weeks, in comparison to the pretreatment baseline level, but this study did use an objective design based on 24-hour EEG/video monitoring. Maximum doses ranged from 4.8 to 9.0 mg/day in this study. In a retrospective study of 24 patients (Volzke et al.. 1967), spasms ceased within 3 weeks in 13 cases (54%) at doses of approximately 1 mg/kg/day. In a number of other smaller trials (10-15 subjects each), cessation of spasms was documented in 20-40% of the patients (Fukushima et al., 1968; Hagberg, 1968; Jan et al., 1971; Chamberlain. 1996). A much higher response rate (82% with cessation of spasms) was reported by Weinmann (1967a) in a retrospective study of 11 subjects, using doses of 7.5-15.0 mg/day. Relapse rates were not provided in most studies, but in two trials spasms recurred in 30-33% of the children.

The above findings suggest that nitrazepam therapy is effective in some patients with infantile spasms, and the reported response rates in the two larger studies are clearly higher than those expected for spontaneous remission. Nitrazepam is not routinely available in the United States, but it is approved for use in a number of other countries.

Commonly reported side effects of nitrazepam therapy included sleepiness, constipation, pooling of oral secretions, urinary retention, insomnia, ataxia, irritability, and hypotonia. Other, more severe, problems noted during these trials included pneumonia, onset of other seizure types, and one death, although these events were not necessarily related to the therapy received.

Clorazepate The anticonvulsant effect of clorazepate is mediated primarily through its metabolite, desmethyldiazepam, which is also a major metabolite of diazepam. Clorazepate has not been systematically evaluated for efficacy in infantile spasms. A single case of infantile spasms was reported in a larger study of clorazepate effectiveness in children with refractory seizures of multiple types, and reportedly this patient had a decrease of spasm frequency (Mimaki et al., 1984). Consequently, no definitive statement can be made regarding the value of this drug in infantile spasms.

Diazepam In spite of the popularity of diazepam in clinical medicine, there have been very few reports of its utility in infantile spasms. A single case was reported as part of a larger trial of diazepam in patients with a variety of seizure types. This patient continued to have spasms in spite of therapy, but with a reduction of seizure frequency (Elian, 1969). In another study of children with myoclonic seizures, the clinical seizures described in two patients were consistent with a diagnosis of infantile spasms, and both were reported to have excellent control of the seizures at doses of 7.5-15.0 mg/day (Weinberg and Harwell, 1965). In the absence of additional information based on larger numbers of subjects, no conclusions can be made regarding the efficacy of this agent for infantile spasms.

Chlordiazepoxide analog (LA-1) The efficacy of 7-nitro-5-phenyl-3H-1-,4-benzodiazepin-2(1*H*)-one, an analog of chlordiazepoxide designated LA-1, was evaluated in two studies which included patients with a variety of seizure types. Markham (1964) reported that 5 of 9 subjects (56%) with infantile spasms had a 90-100% decrease of seizure frequency, while the other trial (Liske and Forster, 1963) found no improvement in 2 subjects with infantile spasms. The most common side effect noted in these studies was sedation. In the absence of more definitive information, the efficacy of this agent remains uncertain.

2.2.2 Valproate

Valproic acid (VPA; 2-propylpentanoic acid or dipropylacetic acid), or its sodium salt, valproate, is a widely used anticonvulsant agent which is effective against a wide spectrum of seizure types. While precise mechanisms of action have not yet been established, there is evidence that administration results in an increase of brain GABA concentration. Other mechanisms may also be important, such as possible suppression of the effects of certain excitatory transmitters (Rowan, 1997). The effectiveness of valproate in infantile spasms has been evaluated in a number of studies conducted since 1975.

In a prospective, blinded, and placebo controlled study of 17 patients who had failed to respond to prior ACTH or corticosteroid therapy, Dyken, et al. (1985), used 6-hour EEG/video monitoring to assess the response. They found no significant difference in the average spasm frequency of patients receiving 2 months of valproate therapy, as compared to those receiving placebo, but did not report the number of subjects of either group who had a complete cessation of

spasms. Two additional prospective studies have been reported. In one (Siemes et al., 1988) involving 22 patients (some newly diagnosed and others after failing to respond to other anticonvulsants), spasms ceased in 50% after 4 weeks (including all 4 cryptogenic cases), and in 68% after 6 weeks, at maximum valproate dosages of 40-100 mg/kg/day, although subsequently 6 of the 15 responders relapsed. In the other study (Pavone et al., 1981), which included 18 patients, 22% achieved complete seizure control within 20 days. In a relatively large retrospective study involving 42 patients (Pavone and Incorpora, 1985) 21% became seizure free (40% of the cryptogenic patients and 11% of the symptomatic subjects), while in two smaller studies (11-14 newly diagnosed subjects) seizure-free response rates of 19% and 43% were reported (Bachman, 1982; Holden et al., 1997). A number of studies involving 3-10 subjects each have been conducted, and in these response rates of 0-50% have been reported (Barnes and Bower, 1975; Dulac et al., 1986a; Nolte et al., 1988; Amano et al., 1990; Ohtsuka et al., 1992; Antoniuk et al., 2000).

The above findings, while quite variable, and inconclusive, suggest that valproate is effective in terms of seizure control in a small fraction of patients with infantile spasms, particularly those in the cryptogenic category.

While severe side effects can be associated with valproate therapy (Rowan, 1997), those reported in association with the above studies were usually mild, and included gastrointestinal distress, sedation, hypotonia, thrombocytopenia, abnormal liver function tests, and hypofibrinogenemia.

2.2.3 Vigabatrin

Vigabatrin (γ-vinyl GABA or 4-amino-5-hexenoic acid) is a relatively new anticonvulsant agent which has proven to be most efficacious in partial seizures. It is a structural analog of the inhibitory neurotransmitter GABA, and its anticonvulsant effect results from an inhibition of GABA-transaminase, with a resultant significant increase of brain GABA levels (Ben-Menachem and French, 1997). Vigabatrin is not routinely available in the United States, but it is approved for use in a number of other countries.

A report appearing in 1989 by Livingston et al. demonstrated the efficacy of vigabatrin in a group of children with refractory epilepsy of various types, and reported a favorable response in several patients with infantile spasms. Subsequently, Chiron et al. (1991) conducted a larger, prospective, trial of vigabatrin including 70 children with refractory infantile spasms. All patients were receiving other medications when vigabatrin was initiated, and 61% had failed hormonal therapy. An overall response rate of 43% (seizure-free) was reported within the 5 month evaluation period, with doses ranging between 50 and 200 mg/kg/day. It was noted that symptomatic patients had a somewhat better response rate (47%) than did the cryptogenic group (36%), and the best results occurred in 14 subjects with tuberous sclerosis, with 10 (71%) becoming spasm-free. An effect of treatment lag was also found, with a better response

rate occurring in those patients treated within 12 months of spasm onset (74%), in comparison to those whose seizures began more than 12 months before therapy with vigabatrin (59%). A number of smaller studies (6 to 23 patients each) of refractory and/or previously treated patients have been conducted over the past decade (Vles et al., 1993; Coppola et al., 1997; Siemes et al., 1998; Zubcevic et al., 1999; Visuditbhan et al., 1999; Tay et al., 2001; Gaily et al., 2001). Overall response rates to vigabatrin have ranged from as low as 13% to as high as 60%, based upon observation periods of 1-8 months. Reported response rates for cryptogenic patients ranged between 33 and 100%, while those for symptomatic cases ranged from 0% to 50%.

In the past 6 years, there has also been considerable interest in the use of vigabatrin as the initial therapy for infantile spasms. In a double-blind, placebo-controlled study of 40 previously untreated children with infantile spasms (Appleton et al., 1999), 35% of the patients exhibited a complete cessation of spasms within 5 days while receiving vigabatrin (50-150 mg/kg/day), while 10% of the placebo group showed a comparable outcome (but both subsequently relapsed). All 40 children then received vigabatrin during a 24-week open treatment phase which resulted in an overall response rate of 36% (56% for the cryptogenic group and 32% for the symptomatic patients). In several other prospective studies (Rufo et al., 1997; Wohlrab et al., 1998; Villeneuve et al., 1998; Granstrom et al., 1999; Fejerman et al., 2000; Elterman et al., 2001), with group sizes of 28-142 subjects, using comparable doses of vigabatrin as the initial therapy, overall response rates were in the 26% to 65% range (50-71% for cryptogenic cases and 19-47% for symptomatic subjects). Comparable overall response rates (47-68%) have also been reported in a number of retrospective trials (Aicardi et al., 1996; Kwong, 1997; Koo, 1999; Antoniuk et al., 2000; Prasad et al., 2001; Kankirawatana et al., 2002; Mitchell and Shah, 2002).

There have been two studies in which the relative effectiveness of vigabatrin and ACTH were compared. In a prospective and randomized study of 42 previously untreated patients, Vigevano and Cilio (1997) reported an overall response rate (spasm cessation) after 20 days of 48% for vigabatrin and 74% for ACTH. A retrospective study of 42 patients conducted by Cossette et al. (1999) found an equivalent response to vigabatrin and ACTH, with 67% of both treatment groups becoming seizure-free after 15 days of therapy.

In addition to the initial report of Chiron et al (1991) noted above, there have been several additional studies suggesting an enhanced degree of vigabatrin efficacy in infantile spasm patients with tuberous sclerosis. In a later prospective, randomized and comparative trial involving 22 subjects with tuberous sclerosis treated for one month, Chiron et al (1997) reported cessation of spasms in 100% of the group receiving vigabatrin (150 mg/kg/day) and in 45% of those receiving hydrocortisone (15 mg/kg/day). Similar results were observed by Elterman et al. (2001) in 23 tuberous sclerosis patients, and by Jambacque et al. (2000) in 7 subjects, with all becoming spasm-free. In a multicenter study (Aicardi et al. 1996), the response rate was 96% for 28

tuberous sclerosis patients, as compared to an overall efficacy of 68% for the entire group of 192 subjects.

The above findings argue strongly for a significant degree of efficacy of vigabatrin in infantile spasms, both as an initial therapeutic agent and in cases in which the spasms are refractory to other drugs. In addition, vigabatrin appears to be particularly effective in children having tuberous sclerosis.

Side effects were sometimes reported in the above studies, the most common of which included drowsiness, irritability, hyperkinesia, insomnia, and hypotonia, but it was only rarely necessary to discontinue treatment. While early animal studies had suggested the possibility of vigabatrin-induced intramyelinic vacuolation or edema, subsequent human investigations did not reveal evidence for its occurrence (Cohen et al., 2000). Encephalopathy has been reported in several patients receiving vigabatrin, including a 6 month old child with complex partial seizures and Alexander disease (Haas-Lude et al., 2000). Recently, concern has been raised due to a number of reports of bilateral concentric visual field constriction in patients receiving vigabatrin (see review by Kalviainen and Nousiainen, 2001). While the cause is still unclear, it may be a result of excessive GABA levels in the retina. The severity of this condition is highly variable across patients, as is the degree to which the visual field defects persist after withdrawal of vigabatrin (in some cases they appear to be permanent, but recovery has also occurred). Approximately 31% of older children and adults receiving vigabatrin are reported to have visual field changes, with the incidence apparently increasing rapidly during the first two years of therapy, and stabilizing by 3 years. In two recent studies which were restricted to subjects less than 18 years old, visual field constriction was reported in 19% of 91 patients by Vanhatalo et al. (2002a) and in 65% of 17 patients by Gross-Tsur et al. (2002). The extent of this problem in very young children is not yet known because of technical problems associated with evaluating visual field status in this group. Consequently, in spite of the apparent efficacy of this drug in infantile spasms, it is not yet clear that the advantages outweigh the potential risks.

2.2.4 Topiramate

Topiramate (2,3:4,5-Di-O-isopropylidine-β-D-fructopyranose sulfamate) is a relatively broad spectrum anticonvulsant agent with reported efficacy in both partial and generalized seizures. While the exact mechanism of action is still unclear, several properties appear to contribute to its efficacy: 1) it acts as an apparent state-dependent sodium channel blocker; 2) it potentiates the effectiveness of the inhibitory neurotransmitter GABA at the $GABA_A$ receptor complex; and 3) it decreases the effectiveness of kainate at the excitatory glutamate receptor, thereby reducing neuronal excitability (Kramer and Reife, 1997). Several studies have examined the usefulness of this drug in infantile spasms.

In a prospective trial which incorporated objective response criteria based on long-term EEG/video monitoring as well as parental observation, Glauser et al. (1998) studied 11 children who had failed to respond to at least two courses of therapy with other drugs. Five of these refractory patients (45%) became seizure-free within 4 weeks of initiation of therapy, with topiramate doses of up to 24 mg/kg/day. This same group (Glauser et al., 2000) also reported a response rate of 33% in a group of 12 patients with refractory infantile spasms evaluated by Y. S. Hwang (previously unpublished data). In a retrospective evaluation of 13 cases of refractory infantile spasms (Herranz, 2000), 15% of the children became seizure-free while receiving topiramate at doses of up to 16 mg/kg/day. In another retrospective study (Thijs et al., 2000), 4 of 7 (57%) refractory patients became seizure-free when topiramate was added to ongoing vigabatrin therapy. However, only 1 of 5 refractory patients studied by Philipi et al. (2002) was controlled by topiramate.

These results, obtained in groups of patients that had proven to be refractory to certain other medications, are encouraging, and suggest that topiramate is efficacious in some cases. We are aware of no studies using this drug that have evaluated its efficacy in newly diagnosed, previously untreated, cases.

Side effects reported in most of these studies were not severe, and included somnolence, other sleep disturbances, lethargy, anorexia, irritability, unsteadiness, increased respiratory rate, and constipation. However, significant metabolic acidosis was documented in 4 of the five patients studied by Philippi et al. (2002), suggesting that acid-base metabolism be monitored in children receiving topiramate.

2.2.5 Ganaxolone

Ganaxolone (3α-hydroxy-3β-methyl-5α-pregnan-20-one) is a member of the epalon class of steroids, which, while lacking hormonal activity, does exhibit anticonvulsant efficacy (Kerrigan et al., 2000; Rogawski and Reddy, 2002). The mechanism of action is apparently related to activation of a specific receptor site on the $GABA_A$ receptor complex present in most cortical neurons. In a preliminary study of ganaxolone efficacy (Monaghan et al., 1999) in children, which included a variety of seizure types, spasm frequency was reported to be decreased by 33-50% in two trials. In a subsequent prospective multicenter trial (Kerrigan et al., 2000) involving 15 subjects with refractory infantile spasms, only one patient became spasm-free (7% response rate) during the 14 week evaluation period, with 33% showing a >50% reduction of spasm frequency. Ganaxolone maintenance doses were in the 18-36 mg/kg/day range during this study. The most common drug-related side effects noted were somnolence, diarrhea, constipation, nervousness, and vomiting. One patient developed mild leukopenia.

These initial results, based upon relatively small studies of refractory patients only, do not permit a meaningful evaluation of the potential value of this drug in the therapy of infantile spasms.

2.2.6 Lamotrigine

Lamotrigine (3,5-diamino-6-(2,3-dichlorophenyl)-*as*-triazine) is a broad-spectrum anticonvulsant drug which has demonstrated efficacy in both generalized and partial seizures. The mechanism of action is unknown, but animal studies have suggested a primary effect on sodium channels, possibly resulting in the regulation or normalization of presynaptic release of excitatory amino acid neurotransmitters. This agent has been evaluated in a very limited number of patients with infantile spasms.

In a prospective study of children with refractory seizures of various types who were treated with lamotrigine (0.5-10 mg/kg/day), two of 13 patients (15%) with infantile spasms became seizure free during a 3-month trial at doses of 0.5-10 mg/kg/day (Schlumberger et al. 1994). In another prospective evaluation of 30 subjects, most of whom were refractory to multiple drugs, 5 children (17%) became seizure-free within 5 months (Veggiotti et al., 1994). A reduction of spasm frequency was observed in a group of 7 patients treated with lamotrigine by Mikati et al. (2002), although none became seizure-free. Low dose lamotrigine (0.15-0.58 mg/kg/day) was reported to be effective in 3 patients previously treated unsuccessfully with ACTH and vigabatrin (Cianchetti et al., 2002). The efficacy of lamotrigine was also evaluated in a group of patients with tuberous sclerosis (previously treated with other drugs), and 29% of 31 children with infantile spasms became seizure-free during the treatment period (Franz et al., 2001). There have apparently been no studies evaluating lamotrigine efficacy in newly diagnosed and previously untreated patients.

Side-effects reported in these studies included somnolence, ataxia, rash, vomiting, headache, and behavioral changes. While there was one death, it was not considered to be drug-related.

Based upon the available evidence, it can not be concluded that lamotrigine has a significant degree of efficacy in this disorder, and the possibility of spontaneous remission can not be excluded.

2.2.7 Zonisamide

Zonisamide (1,2-benzisoxazole-3-methanesulfonamide) is a drug of the sulfonamide class and has been shown to have efficacy against partial seizures in a number of studies. Several studies have also demonstrated improvement in patients with generalized seizures. The mechanism of action is unknown, but evidence suggests that it may involve both blockage of sodium channels and reduction of voltage dependent calcium currents, resulting in suppression of

neuronal hypersynchronization (Seino and Ito, 1997). The efficacy of this drug in infantile spasms has been evaluated in several studies.

A prospective, multicenter, study of zonisamide (Suzuki, 2001) which included 54 newly diagnosed infantile spasms patients found an overall response rate of 20% (cessation of spasms and disappearance of hypsarrhythmia) within 3 weeks. The response was slightly better in the cryptogenic group (29% of 14 subjects), as compared to the symptomatic group (18% of 40 patients). Zonisamide doses of 3-13 mg/kg/day were used in this study, and all patients had failed to respond to an initial trial of pyridoxine (30-50 mg/kg/day). It was noted that 3 of the 11 responders experienced a recurrence of spasms after 4-10 weeks. Four additional smaller trials (9-27 cases each) have reported similar response rates (25-38%) at comparable dosages (Hikima et al., 1993 [as reviewed in Suzuki, 2001]; Yanagihara et al., 1995; Yanai et al., 1999; Kawawaki et al., 1999). No serious side effects were reported during these studies (one patient experienced drowsiness).

While the reported response rate to zonisamide therapy is low (20-38%), most patients have responded within a relatively short time (typically 1-3 weeks), and so it seems probable that this drug is effective in a subset of children with infantile spasms.

2.2.8 Felbamate

Felbamate (2-phenyl-1,3-propanediol dicarbamate) is structurally similar to meprobamate, and is reported to have a very broad spectrum of anticonvulsant activity (Theodore, 1997). The mechanism of action is unclear, but in vitro studies have suggested that it blocks NMDA-dependent (*N*-methyl-D-aspartate) currents while facilitating GABA responses.

The efficacy of felbamate as an add-on therapy in children with infantile spasms refractory to other medications has been evaluated in several small trials. Hurst and Rolan (1995) reported that 3 of 4 subjects (75%) became seizure-free within 2-3 days at dosage levels of 15-30 mg/kg/day, while in a study of 11 patients (Hosain et al., 1997) seizures were eliminated in only 1 of 11 children (9%) at dosages of 15-75 mg/kg/day. Spasms continued in all 8 subjects in a study by Cilio et al. (2001). There have been no studies reporting the efficacy of this drug in previously untreated patients.

The most frequent side effects reported were anorexia, weight loss, urinary retention, somnolence, nervousness and insomnia. A single death was reported during these studies, although the cause was undetermined. However, severe, sometimes fatal, side effects have been reported in other patients receiving felbamate, including aplastic anemia and hepatic failure.

In view of the inconclusive evidence for a significant degree of efficacy, and the potential for severe side effects, the routine use of this drug as a therapy for infantile spasms is not recommended.

2.2.9 Miscellaneous Anticonvulsants

While it is commonly believed that most of the older (i.e. available prior to 1960) anticonvulsants are not effective in controlling infantile spasms (Jeavons and Bower, 1964), there have been surprisingly few studies that either support or refute this conclusion. **Phenobarbital** was found to have little efficacy (14% spasm-free rate), and both **milontin** and **gemonil** had no efficacy (0% response rate) in a retrospective evaluation (Baird and Borofsky, 1957), but here have been no subsequent trials of these agents. We are aware of no systematic studies of **carbamazepine**, although apparent effectiveness has been noted in several case reports (Koide and Shime, 1993; Miyazaki et al., 1994b). Many other agents have been used in clinical practice, but have not been systematically evaluated.

2.3 Other Agents

2.3.1 Vitamin B_6 (Pyridoxine, pyridoxal, pyridoxamine)

Vitamin B_6 is involved in multiple metabolic pathways, and consists of three forms: pyridoxine, pyridoxal and pyridoxamine, all of which are converted to the coenzyme pyridoxal-5-phosphate (Toribe, 2001). While vitamin B_6 deficiency and vitamin B_6 dependency can be associated with seizures, most cases of infantile spasms do not fall into these categories, and consequently the mechanism of action of high-dose vitamin B_6 in this disorder is not clear. A possible involvement of vitamin B_6 in GABA regulation has been suggested (Kurlemann et al., 1997), based upon an observed normalization of CSF GABA levels following treatment in a single case of infantile spasms. Vitamin B_6 is also known to be involved in many other metabolic pathways, including those regulating serotonin synthesis (see Chapter 10, section 2.4).

In a large retrospective study which included 216 cases, 14% became seizure-free within 20 days at doses of 30-400 mg/day (Ohtsuka et al., 1982, 1987, 2000). The response was better in cryptogenic patients (30%) than in the symptomatic group (11%). In several prospective trials involving both newly diagnosed cases and patients treated previously with other agents, with group sizes of 17 to 50 patients, reported response rates have ranged between 3% and 29%, with doses of 20-300 mg/day and treatment durations of 3 to approximately 30 days (Pietz et al., 1993; Heiskala et al., 1996; Hirai et al., 1998; Takuma 1998; Toribe, 2001). In these studies, the cryptogenic patients did not consistently fare better than the symptomatic cases. Relapse rates of 0-33% were reported. Side effects were infrequent, and included decreased appetite, restlessness, crying, and apathy. While therapy has typically been continued indefinitely in responsive subjects, seizures frequently do not recur if it is discontinued (Ohtsuka et al., 2000).

The efficacy of a single IV dose of pyridoxine (300 mg) was evaluated in 33 patients prior to institution of ACTH therapy, with continuous EEG monitoring (Fois et al., 1987). No EEG improvement was observed in any of the cases.

While the reported efficacy has been low in most studies, the fact that when response does occur it is typically within a few days to weeks suggests that there is a subset of patients for whom this therapy may be beneficial. The major potential advantage is the low frequency of severe side effects.

2.3.2 Thyrotropin-releasing hormone (TRH)

Thyrotropin-releasing hormone (TRH; L-pyroglutamyl-L-histidyl-L-prolineamide) is a member of the group of hypothalamic-releasing hormones, and is found in many brain regions (Takeuchi et al., 2001). It has been used successfully to treat several pediatric neurological disorders in addition to epilepsy, although the basis for its efficacy is still unclear. Its role as an anticonvulsant agent may be related to an influence on monoamine metabolism, possibly including a potentiation of the inhibitory effects of serotonin and dopamine. In support of this hypothesis, Takeuchi et al. (1999) found a decreased CSF level of kynurenine (a metabolite of tryptophan and precursor of kynurenic acid, which is itself an antagonist of certain excitatory receptors) in a group of infantile spasms patients. The therapeutic effect of TRH in infantile spasms has been evaluated in several studies.

In a prospective trial which included 17 subjects, administration of TRH at doses of 0.5-1.0 mg/day for up to 4 weeks resulted in a response rate (cessation of spasms) of 47% (Matsumoto et al., 1989). Takeuchi et al. (2001) reported that 5 of 16 patients (31%) became seizure free in a 1-3 month trial with a TRH dose of 0.05 mg/kg/day. The relative efficacy of TRH and ACTH were compared in a prospective study of 33 subjects (Matsumoto et al., 1987), with 75% of the patients receiving ACTH becoming spasm-free, in contrast to 54% of the TRH group. An analog of TRH (DN-1417) was administered to two patients in a pilot study, but neither improved (Matsuishi et al., 1983). No significant side effects were reported in these studies.

These findings suggest that TRH therapy is effective in some patients with infantile spasms, and the reported response rates for the relatively short trial durations are clearly higher than those expected for spontaneous remission.

2.3.3 Immunoglobulins

The use of pooled human immunoglobulins (primarily IgG) as a therapy for a variety of seizure disorders is largely empirical, but is generally based on experimental data from animal studies suggesting involvement of the immune system in some seizure models (Delire, 1997). The efficacy of intravenous immunoglobulin (IVIG) therapy in infantile spasms has been specifically evaluated in several studies.

In a prospective study involving 11 patients (Ariizumi et al., 1987), 82% of the patients became seizure-free after receiving 1-8 doses of IVIG (100-200mg/kg) spaced at 2-3 week intervals. All six cryptogenic patients were among the responders, as were 3 of 5 (60%) symptomatic patients. The relapse rate was 22% (all symptomatic patients). A much lower response rate of 26% was reported in another prospective study (Echenne et al., 1991) of 19 patients (400 mg/kg/day for 5 days every 6 weeks, or 1g/kg/day for 2 days every 3 weeks; total duration approximately 6 months), although this study was terminated after 6-8 days if no response was achieved, and the subjects were switched to ACTH. Response rates of 25-43% have been observed in several smaller trials (Shiihara et al., 1984; van Engelen et al., 1994; Espinosa-Zacarias et al., 2002). No significant side effects were reported in these studies.

These findings suggest that immunoglobulin therapy is effective in some cases of infantile spasms.

2.3.4 Methysergide, AMPT, Tetrabenazine, and PCPA

As a test of the hypothesis that infantile spasms could be a result of increased activity within brainstem adrenergic and/or serotonergic neuronal populations (see Chapter 10), we conducted trials of several agents known to interfere with these neurotransmitter systems. During a 3 week trial of α-methylparatyrosine (AMPT), a competitive antagonist of tyrosine hydroxylase, using doses of 500-1250 mg/m^2/day, 2 of 12 previously untreated subjects (17%) became seizure-free and exhibited EEG improvement, although one subsequently relapsed (Hrachovy et al., 1989). Methysergide, a serotonin receptor blocker, was also tested in 12 newly diagnosed subjects (2-5 mg/m^2/day for 3 weeks), with one patient (8%) becoming seizure-free (Hrachovy et al., 1989). However, this patient subsequently relapsed. In a study of tetrabenazine (15 mg/m^2/day for 3 weeks) which included 12 subjects (7 previously untreated and 5 newly diagnosed), there were no responders (Hrachovy et al., 1988b). No side effects were observed in these studies.

In an earlier study by Coleman et al. (1971), both methysergide and parachlorophenylalanine (PCPA) were found to be ineffective in 3 patients with infantile spasms in whom there was evidence for abnormalities of the serotonin metabolic pathway (i.e., elevated blood serotonin levels and increased efflux of serotonin from platelets). They concluded that elevated endogenous serotonin was not likely to be the primary disease process in the central nervous system.

The results of these studies do not suggest a significant degree of efficacy for any of these drugs.

2.3.5 Barbiturate Anesthesia

Following anecdotal reports of cessation of infantile spasms after routine surgical procedures (Riikonen et al., 1988), the effect of barbiturate anesthesia

has been evaluated in several studies. Brief thiopental anesthesia (approximately 30 min) produced no lasting improvement in 5 patients studied prospectively by Riikonen et al. (1988). In a larger trial (Rantala et al., 1999), 24 children with infantile spasms received 4-5 days of thiopentone anesthesia. While spasms stopped in all subjects during anesthesia, only one patient (4%) continued to be seizure-free during subsequent follow-up. Finally, two of 3 patients became seizure-free after 4-5 days of thiopentone anesthesia in a study by Eriksson et al. (1993).

Based on the available evidence, this treatment modality does not appear to be significantly efficacious.

2.3.6 Miscellaneous Agents

A number of other agents have been evaluated in single trials, most of which involved relatively few subjects. **Acetazolamide** (Diamox), a potent carbonic anhydrase inhibitor useful in some seizure disorders, was reported to be ineffective in infantile spasms, with no improvement observed in 16 treated patients (Baird and Borofsky, 1957). This same group also evaluated the amino acid **asparagine** in 15 patients, and none became spasm-free. The acute effects of **naloxone** (a narcotic antagonist) were evaluated in 5 subjects following IV injection, and no effect on EEG characteristics was observed in any patient during a 2-hour period (Nalin et al., 1988). A single patient with infantile spasms was treated with **allopurinol** (a xanthine oxidase inhibitor), but no improvement was documented (Tada et al., 1991). A patient with low CSF homovanillic acid levels, suggesting impaired dopamine metabolism, was successfully treated with oral **L-dopa**, with long-term control of spasms (Sugie et al., 1989). Seizures were controlled in 7 of 12 patients (58%) treated with **sulthiame**, following initial therapy with pyridoxine (Debus et al., 2002). **$ACTH_{4-10}$**, an ACTH fragment without adrenocortical stimulatory effects, was found to be ineffective in all 4 subjects treated (Willig and Lagenstein, 1982). A single patient with pyruvate dehydrogenase complex deficiency and infantile spasms had a marked decrease of spasm frequency when treated with **dichloroacetate** (Harada et al., 1996). Finally, the effect of **pyretotherapy** (elevated temperature for 48-72 hours induced by administration of typhoid/paratyphoid vaccine) was tested in 4 subjects with infantile spasms, all of whom were reported to have a decrease of spasm frequency (Garcia de Alba et al., 1984).

2.4 Special Diets

In an early study of the treatment of infantile spasms, Baird and Borofsky (1957) reported that 3 patients placed on a **ketogenic diet** improved, but that compliance could not be maintained. In a recent retrospective evaluation of this therapy (Nordli et al., 2001), reported that 6 of 17 patients (35%) became

seizure-free within several months. In a study by Kossoff et al. (2002), 13 of 23 patients (57%) remained on the diet for at least 12 months, and, of these 13, only 3 (23%) were seizure-free. There have apparently been no prospective and/or long-term studies of this treatment, and so its relative value in infantile spasms remains unclear.

In a study of 17 patients diagnosed with phenylketonuria who also had infantile spasms (Zhongshu et al., 2001), institution of a **low phenylalanine diet** alone resulted in cessation of spasms in all cases (100%), but 78% of these patients subsequently relapsed. Previously Baird and Borofsky (1957) studied the effectiveness of a **tryptophan deficient diet** in 3 patients with infantile spasms, but without a diagnosis of any specific metabolic disorder. Spasms continued in all cases, although improvement was noted in one case. A patient with documented histidinemia and infantile spasms resistant to multiple medications did not respond to a **low histidine diet** (Duffner and Cohen, 1975).

3. SURGICAL THERAPY

3.1 Discrete anatomical lesions

Several case reports have appeared over the years describing the occurrence of discrete anatomical lesions in association with infantile spasms. These lesions have included a choroid plexus papilloma (Branch and Dyken, 1979), a tumor (fibromatosis with myofibroblastic invasion) of the tentorium cerebelli (Dolman et al., 1981), a temporal lobe astrocytoma (Mimaki et al., 1983), an anaplastic ependymoma (Ruggieri et al., 1989), a frontal lobe tumor (Wyllie et al., 1996a), and porencephalic cysts (Palm et al., 1988; Uthman et al., 1991). In all cases, significant improvement of the patient's condition followed surgical treatment, and in several instances spasms previously refractory to medical therapy ceased.

3.2 Surgery for medically intractable infantile spasms

Spiegel et al. (1958) reported the successful surgical treatment of 4 out of 5 patients with medically intractable infantile spasms through the use of stereotaxic pallidotomy or pallidoamygdalotomy. Depth electroencephalographic recordings in these patients had shown seizure discharges in the basal ganglia which had variable time relationships to simultaneously recorded scalp discharges, and the investigators postulated that the efficacy of this approach could be due to interruption of corticofugal impulses arising in the basal ganglia, or to elimination of subcortical foci. Shields et al. (1990) described 8 patients with a history of infantile spasms (4 were continuing to have spasms, while the other 4 had only partial seizures) who had evidence of a focal cortical lesion (by EEG, MRI, CT, or PET) at the time of evaluation. Following hemispherectomy or focal cortical resection, 5 patients were seizure-free, including 3 who had been having spasms prior to surgery.

Interest in the surgical treatment of infantile spasms intensified in 1990 with the report of Chugani et al. (1990) describing control of seizures in 4 cryptogenic patients following focal cortical resections. These 4 patients were selected from a larger group of cryptogenic patients with medically refractory seizures and normal MRI and CT studies because they exhibited unilateral, localized, hypometabolism (glucose utilization) by positron emission tomography (PET). During surgery, electrocorticography was used to delineate the extent of the resection, which reportedly corresponded closely to the PET-defined hypometabolic region. Microscopic examination of tissue removed at surgery was consistent with cortical dysplasia in all cases. While all of these patients were having seizures of some type prior to surgery, not all were still having spasms. EEGs showed focal abnormalities in all subjects, and none had hypsarrhythmia at the time of the PET study. This same group (Chugani et al., 1993) expanded their original study to include a total of 23 medically intractable subjects who showed focal or lateralized PET abnormalities (18 with localized hypometabolism, 5 with focal hypermetabolism). Only 9 of these subjects had abnormalities by CT and/or MRI. All patients initially had infantile spasms, but in 6 cases spasms had ceased prior to surgery (these 6 patients continued to have seizures of other types). All patients had focal EEG findings, which typically corresponded to the area identified by the PET findings. A focal resection was carried out in 15 of these patients, and a hemispherectomy was performed in the other 8 patients, who exhibited diffuse or multifocal lateralized PET abnormalities. Fourteen patients (61%) were reported to be seizure-free at follow-up, an average of 28 months later (range 4-67 months). Six of the controlled patients continued to receive anticonvulsants. Pathological examination of the resected tissue revealed abnormalities in 22 of the 23 patients, with cortical dysplasia being the most common finding.

In a study evaluating temporal and extended temporal surgical resections in a variety of childhood epilepsies (Adelson et al., 1992), 5 of 6 patients with infantile spasms (83%) were seizure-free at follow-up, a minimum of 18 months after surgery. Development was said to be improved in all cases. All of these patients had one or more abnormal imaging studies (MRI, CT, or PET) prior to surgery indicating the presence of a localized process. Pathological studies of the resected tissue revealed either architectural abnormalities (including cortical dysplasia) or reactive changes in all subjects. Similarly, Hoffman (2001) reported that 5 of 11 (45%) infantile spasms patients with focal cortical dysplasia became seizure-free following hemispheric decortication.

A retrospective study designed to assess the relative frequency of focal features in patients with infantile spasms (Kramer et al. 1997a) evaluated 67 cases treated between 1989 and 1992. The analysis revealed that 66% of the patients had at least one focal feature, including lateralized EEG findings (42%), hemiparesis (30%), asymmetric imaging (MRI or PET) findings (27%), asymmetric spasms (20%), and partial seizures (51%). Nine patients underwent

resective (hemispherectomy or corticectomy) surgery, and 6 (67%) reportedly became seizure-free (one subject died during surgery).

A single case report (Wyllie et al. 1996b) also provides evidence for the efficacy of focal cortical resection based upon a PET-defined abnormality. This patient had hypsarrhythmia and MRI evidence for a diffuse insult (bilateral periventricular leukomalacia and germinal matrix hemorrhage), but became seizure-free following a right temporo-parieto-occipital resection.

Two patients with symmetrical infantile spasms and bilateral hypsarrhythmia refractory to multiple drugs underwent total callosotomy (Pinard et al. 1993). In both cases, while seizures continued to occur, the spasms became asymmetrical, and the hypsarrhythmia became unilateral, suggesting that the corpus callosum is important in determining the clinical expression of infantile spasms.

A very important aspect of the above studies is the demonstration that a subset of patients with infantile spasms, including some in the cryptogenic category, has demonstrable focal features evident on metabolic imaging, and that these focal areas typically correspond to underlying cortical pathology. While surgical resection of these areas has been correlated with improved seizure control in a limited number of cases, the currently available data do not permit a definitive statement to be made regarding the relative efficacy of this type of surgical treatment as compared to conventional medical management. One significant limitation is the fact that in most of the studies of surgical efficacy the response rate was based on patient status 1-2 years, or even longer, following surgery, whereas studies evaluating response to medical therapy have typically documented seizure status within a few weeks to months after initiation of treatment. Since spontaneous remission is a significant factor in this disorder, particularly over time periods of 1-2 years, it is likely that it plays a role in the reported results. Other limitations of the current data include the fact that infantile spasms and/or hypsarrhythmia had ceased in some cases prior to the surgical procedure, and that most patients continued to receive medical therapy after the surgical resection. Finally, because of the risk associated with surgery, studies to date of cryptogenic subjects have, by necessity, been restricted to those patients proven to be refractory to one, or more, drugs. However, in spite of these limitations, the surgical approach, and the techniques upon which it is based, are clearly encouraging and suggest that it may contribute significantly to improved management of this disorder. In addition, as discussed in Chapter 12, there is the hope that this therapy may be associated with improved long-term prognosis for mental development.

4. DISCUSSION AND SYNTHESIS

Based upon the above analysis, no single drug, or other treatment modality, clearly stands out as having a major advantage in terms of efficacy for the control of infantile spasms. Surgery may be the treatment of choice in the small number of patients in which certain discrete structural lesions are present, but in

the majority of instances this is not the case, and the potential advantages of surgery in these other infants are still uncertain. In spite of intense interest generated in recent years by encouraging results with several of the newer anticonvulsants, ACTH, and the corticosteroids, appear to be equally efficacious and have been more widely used in clinical practice. However, vigabatrin, while offering no significant advantages in comparison to ACTH in most cases, does appear to be more efficacious than any other mode of therapy for control of spasms in children with tuberous sclerosis. While a number of other anticonvulsants and other drugs have also exhibited some degree of efficacy, none have consistently been associated with response rates exceeding ACTH, corticosteroids or vigabatrin, although many have not yet been thoroughly evaluated.

Perhaps the most interesting aspect to emerge from the large number of therapeutic trials that have been conducted is the overwhelming evidence that patients who do not respond to one form of therapy may quickly respond to another. The response rates reported for most agents are not consistently lower in trials which include patients refractory to prior treatment with other drugs, in comparison to trials comprising only newly diagnosed, previously untreated, subjects. In other words, failure to respond to one therapeutic modality does not seem to predict response to another. This pattern has also been observed in several prospective studies which used a crossover design. For example, in our crossover study comparing ACTH and prednisone (Hrachovy et al., 1983), 42% of patients receiving ACTH as the initial drug responded, as did 50% of the infants who initially failed to respond to prednisone. Conversely, 33% responded to prednisone as the initial drug, compared to a 43% response in patients who did not respond to initial ACTH therapy.

One conclusion that could be drawn from these observations is the concept that the entity designated as infantile spasms, or West syndrome, actually consists of multiple subcategories with different underlying pathophysiologies, each of which will respond only to certain therapeutic agents. This is a reasonable explanation, since it is clear that this disorder is apparently triggered by a wide variety of known etiological factors (Chapter 10), in addition to others currently classified as cryptogenic or unknown. If this concept is true, the implications for therapeutic planning are obvious: best results should be achieved through a systematic application of multiple therapeutic modalities, until a favorable response is achieved.

5. RECOMMENDED APPROACH TO TREATMENT

Based upon our analysis of the studies summarized in this chapter, several therapeutic modalities were identified that appear to have efficacy in this disorder. These modalities are listed in Table 11.4, along with their associated implementation parameters. For the reasons discussed in the preceding section, it is not currently possible to predict whether or not a particular patient will

Table 11.4 **Therapeutic modalities with demonstrated efficacy in infantile spasms and suggested parameters for implementation**

Therapy	*Initial dose*	*Maximum Maintenance dose*	*Minimum duration of therapy*	*Maximum duration of therapy if no response*	*Continue therapy if response occurs?*
ACTH	20 u/day	30 u/day	2 weeks (plus 1 week taper)	6 weeks (plus 1 week taper)	No
Corticosteroid (prednisone)	2 mg/kg/day	2 mg/kg/day	2 weeks (plus 1 week taper)	6 weeks (plus 1 week taper	No
Vigabatrin **	50 mg/kg/day	200 mg/kg/day	N/A	8 weeks	Yes *
Nitrazepam **	1 mg/kg/day	10 mg/kg/day	N/A	12 weeks	Yes *
Valproate	40 mg/kg/day	100 mg/kg/day	N/A	8 weeks	Yes *
Pyridoxine (vitamin B_6)	100 mg/day or 20mg/kg/day	400 mg/day or 50mg/kg/day	1 week	2 weeks	Yes *
Topiramate	12 mg/kg/day	24 mg/kg/day	N/A	8 weeks	Yes *
Zonisamide	3 mg/kg/day	13 mg/kg/day	N/A	6 weeks	Yes *
Immunoglobulin	100 – 400 mg/kg/day x 1-5 days	400 mg/kg/day x 5 days every 6 weeks	5 days	8 weeks	Yes, up to 6 months
TRH	0.05 – 0.5 mg/kg/day	1.0 mg/kg/day	2 weeks	4 weeks	No
Surgery	N/A	N/A	N/A	N/A	N/A

N/A Not applicable to this form of therapy
* An attempt at discontinuation is suggested after several months
** These drugs are not approved for general use in the United States

respond to a particular drug or surgical approach. Consequently, a systematic approach to the management of this disorder is recommended, in which all available information regarding the patient's status is used to guide the initial therapeutic choice, and if necessary, other modalities are subsequently evaluated in a predetermined and logical sequence.

A suggested therapeutic protocol is summarized in Fig. 11.4, and, when used in conjunction with Table 11.4, provides a logical and time-limited approach to the management of infantile spasms. The goal is to achieve control of the spasms as quickly as possible, and the key factor is avoidance of unnecessarily prolonged treatment with agents that are ineffective. Thus, if one modality does not lead to seizure control within a specified time interval, it is withdrawn and a new trial is initiated using another agent and a set of therapeutic parameters appropriate to the new drug. The major features of this approach are outlined below:

5.1 Initial Decisions

As indicated in Fig. 11.4, the initial therapeutic decision is based upon careful consideration of all available diagnostic information, including the baseline EEG and imaging studies. At this stage, it is crucial to identify any patient with a lesion requiring immediate surgical resection (see section 3.1, above). Subjects with focal or lateralizing features who do not have evidence of a discrete lesion necessitating prompt removal are also identified to facilitate future reconsideration of a surgical approach if medical treatment is not successful. These patients, as well as subjects with no focal features, then begin the systematic medical protocol.

5.2 Medical Protocol Implementation

The choice of an initial drug is left up to the clinician, with the major options listed in Table 11.4. While our choice is usually ACTH as the first drug, other agents are preferred by other investigators, and, as previously discussed (Section 4) no drug can be clearly identified at present as being the most likely to produce a favorable response. Vigabatrin has been proposed as the initial drug of choice by some in the case of concurrent tuberous sclerosis, but recent questions regarding visual side effects have tempered this enthusiasm. Many physicians prefer to start with pyridoxine, since it can be evaluated quickly, and because of relatively few side effects. However, the choice of an initial drug is probably less important than is the adherence to a structured protocol which permits multiple agents to be evaluated efficiently, if necessary.

Table 11.4 summarizes the suggested parameters for implementation of the therapeutic protocol. For example, if ACTH is chosen, the drug should be started at a dosage of 20 u/day (Table 11.4, column 2, *Initial dose*) and continued for 2 weeks (column 4, *Minimum duration of therapy*). If a response (i.e., cessation of spasms and improvement of the EEG) is documented at that time, ACTH is tapered to zero over 1 week, and therapy is discontinued (column 6, *Continue therapy if response occurs?*). If a response is not documented at 2

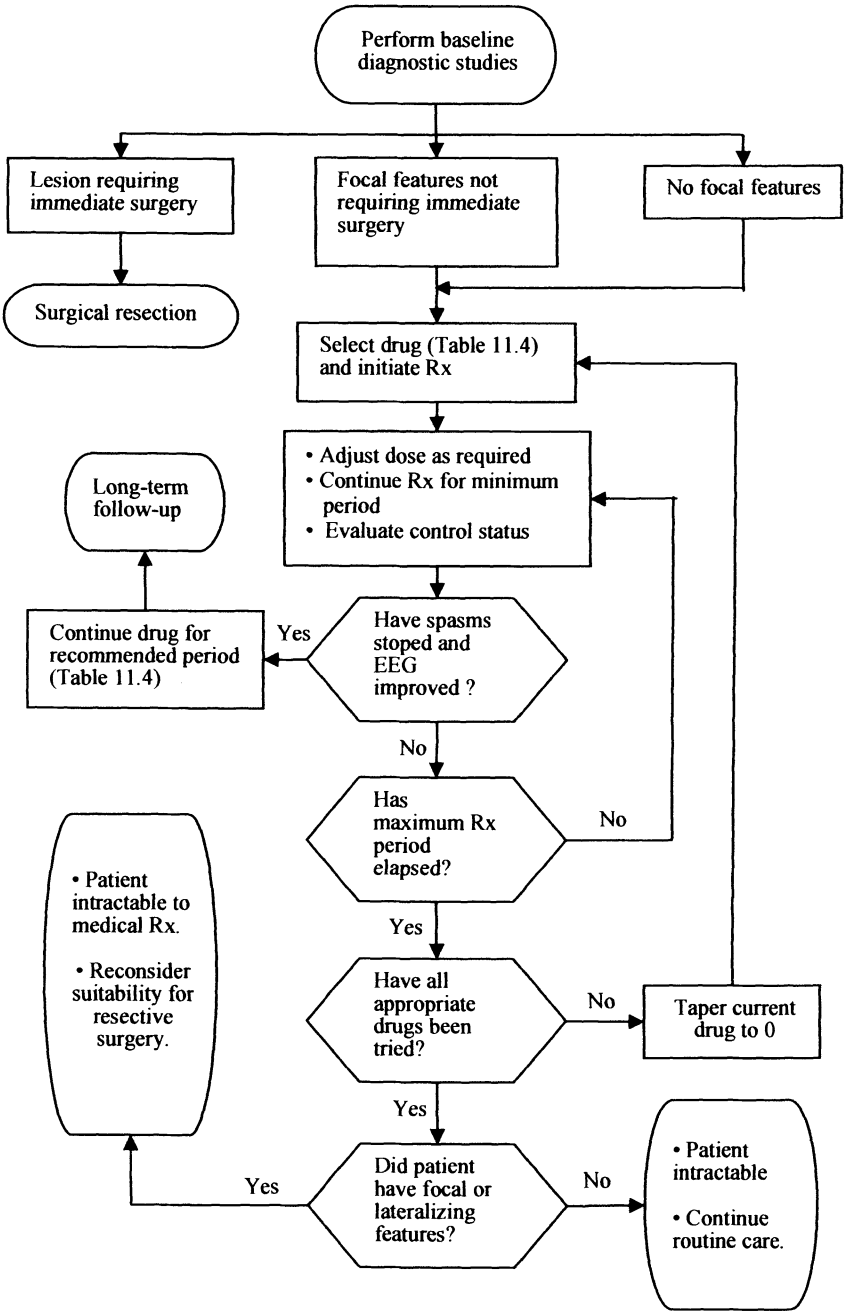

Figure 11.4 Flowchart summarizing recommended approach to the management of infantile spasms.

weeks, the dosage should be increased to 30 u/day (column 3, *Maximum maintenance dose*) and treatment continued for another 4 weeks (column 5, *Maximum duration of therapy if no response*), and then tapered to zero. If a response is documented at 6 weeks the patient then enters long-term follow-up; if spasms continue, the physician chooses another drug from Table 11.4, and initiates a new treatment trial (Fig. 11.4).

For several of the drugs listed in Table 11.4 (vigabatrin, nitrazepam, valproate, topiramate, and zonisamide) a minimum duration of therapy is not specified (column 4), and these anticonvulsants should be continued for at least the maximum duration specified (column 5), whether a response occurs or not. For example, if valproate is chosen the initial dose of 40 mg/kg/day is gradually increased over a period of several weeks until a response occurs, or the patient becomes intolerant to the increased dose, or the maximum maintenance dose is reached. The highest dose level thus attained is then continued for the duration of the treatment trial. If the spasms are not controlled at the end of the maximum duration of therapy specified in column 5 of Table 11.4, the drug is discontinued and a new modality selected. If the patient does respond to this therapy, treatment is continued for an indefinite period at the current dosage (an attempt at discontinuation is suggested after several months of therapy).

This protocol follows closely the standard approach to the management of infantile spasms taken by most clinicians. It differs primarily by the establishment of specific time limits on the duration of therapy with any one agent, and by the more systematic use of multiple agents.

5.3 Determination of Response

Successful implementation of this therapeutic protocol is critically dependent upon the ability to determine if spasms have ceased, and the EEG has improved. The problems inherent in this decision making process have been discussed previously (Section 1.2, above), and the risks of depending solely on subjective observation by parents or other caregivers were emphasized. Consequently, we believe that an apparently successful response to a particular therapeutic modality should always be confirmed by 24-hour EEG/video monitoring. This will maximize the overall efficiency of the therapeutic protocol, and minimize the time required to determine the optimal therapy.

If long-term EEG/video monitoring is not available, or if third party insurers will not pay for this study, the clinician may be forced to rely on parental, or other caregiver, observation to determine spasm frequency. In this instance, cessation of spasms may be assumed to have occurred if the caregiver has not observed spasms for at least 5 consecutive days. During this observation period the caregiver must observe the patient at various times throughout the day and night, and must be in attendance during times when the infant arouses from sleep. If the caregiver has not observed any spasms for 5 consecutive days, a repeat EEG, including sleep, should be performed. If the hypsarrhythmic pattern

has disappeared at that time, it can be assumed, but not proven, that a response to therapy has occurred.

5.4 Long-term Follow-up

After a response to a particular drug is documented, the patient is withdrawn from the treatment protocol, and followed at routine intervals appropriate to the subject's overall medical condition. Some medications are discontinued at that time (e.g., ACTH) since seizure control is typically maintained, and no added benefit from long-term therapy has been proven. Other medications, including the standard anticonvulsants (e.g., valproate) are continued at the effective dose. However, we recommend that such drugs be withdrawn after several months in order to determine if continued therapy is still warranted. If spasms recur, then the medication is reinstituted at the previously effective dose; otherwise, the patient is followed routinely.

If spasms later recur in a patient who has been withdrawn from the effective medication, the protocol (Fig. 11.4) should be reinstituted, starting with the previously effective drug. If a relapse occurs in a patient still receiving the drug previously determined to be effective, the therapeutic protocol should be reinstituted using another agent selected from those listed in Table 11.4.

5.5 Management of Medically Intractable Patients

If all available drugs are evaluated within the therapeutic protocol (Fig. 11.4) without success, it can be concluded that the patient is intractable to medical therapy, and it is unlikely that continued treatment with any of the agents will be of benefit. At this point, it is reasonable to reconsider the possibility of resective surgery in the subset of patients that demonstrated focal or lateralizing features during the original diagnostic work-up. Additional imaging studies may be indicated, including PET, which may provide more definitive information regarding the possibility of a successful surgical approach.

6. FUTURE RESEARCH

Many unanswered questions remain regarding the treatment of infantile spasms. While a very large number of studies have been published on this subject, the vast majority have involved small numbers of subjects, have been uncontrolled or retrospective, and very few have used objective measures to document response (Table 11.1). In addition, widely different treatment parameters have been used, both in terms of dosages and with respect to duration of treatment prior to determination of response status. Also, it has not been determined how long therapy should be continued following documentation of a response for all agents, with the exception of ACTH and corticosteroids. Consequently, while a number of drugs appear to have efficacy (Table 11.4),

there is no definitive information regarding relative efficacy, and, with the possible exception of vigabatrin and tuberous sclerosis, no information to allow preselection of specific drugs for specific subgroups of infantile spasms exists.

Thus, there is clearly a need for well-controlled, prospective, blinded studies evaluating the relative efficacies of all of the currently recognized drugs. Such studies can provide definitive information only if they include large enough patient populations to permit meaningful statistical analysis, and also incorporate long-term EEG/video monitoring in an experimental design that allows an objective determination of response, as defined by complete control of the spasms and improvement of the EEG (i.e., disappearance of the hypsarrhythmic pattern). This can probably only be accomplished by utilizing large multicenter trials.

There is also a need for more information regarding the optimal therapeutic approach to this disorder. The treatment protocol described above (Section 5) is based on available information, both published and unpublished, which suggests that this approach provides the most efficient course. However, it has not been tested in a prospective design, and the overall response rate to be expected is unknown.

It is also not clear whether subpopulations of infantile spasms patients responsive to different therapeutic agents truly exist, or whether therapeutic response is actually more of a statistical process, dependent on a common triggering effect which might simply fail on one try and succeed on another. This possibility is supported by the well-established concept that when a subject does respond to ACTH or corticosteroids, it is often possible to discontinue therapy within a short time while seizure control persists indefinitely, suggesting that the initiation of treatment simply triggered some physiologic process, which then became self-sustaining. This possibility is also supported by the observation that if a relapse does occur, a second course of hormonal treatment with the same agent will often result in re-establishment of control. Thus, it is conceivable that a subject failing a particular therapeutic modality might respond favorably to a second (or even third or fourth) course, or "pulse" of the same agent. In such cases, it could be the initial rapid rise in drug (or metabolite) levels within the CNS that acts as the trigger, and, if control does not occur immediately, subsequent sustained levels of the drug would be ineffective. If this pulse hypothesis is true, then many of the drugs that have been identified as efficacious in this disorder may actually be equivalent in terms of their mechanism of action. There is currently no experimental evidence for this concept, and, to our knowledge, there have been no therapeutic trials in which the subjects who failed to respond to a particular drug were withdrawn from it for a short time, and then given a second trial of the same agent.

Finally, there is a need for more information, based on well-controlled, prospective studies, using objective measures of seizure control, concerning the efficacy of surgical resection of metabolically defined foci in those patients without classical surgical lesions. This approach has been proposed as possibly

offering not only improved seizure control in some patients intractable to medical therapy, but also more favorable long-term outcome (see Chapter 12).

Chapter 12

Long-Term Outcome

1. BACKGROUND

The prognosis in West syndrome is poor overall, although a small number of individuals recover, with both resolution of seizures and achievement of normal mental development. While the natural history of this disorder is, in general, well documented, major questions remain unanswered regarding the factors that influence, or predict, outcome, and the long-term benefits of various therapeutic modalities. As discussed in the preceding chapter, a number of therapies have demonstrated efficacy for the control of spasms and improvement of the EEG characteristics. In this chapter, the evidence for an effect of such treatment on long-term outcome is considered, and we attempt to distinguish changes that are simply a part of the natural history of the disorder from those that are truly associated with therapeutic intervention.

As with trials of initial treatment efficacy, most studies assessing long-term outcome have been plagued with numerous methodological shortcomings that make it difficult to derive clear-cut answers to the various questions regarding factors that influence prognosis. For example, many studies have been retrospective, have included a wide spectrum of etiological factors, as well as inconsistent treatment protocols, and often have included patients treated with a variety of agents. But, perhaps the most serious difficulty encountered in evaluating the majority of published studies is the failure to provide outcome measures at standardized times following institution of treatment, or even at specific chronological ages. Thus, studies are encountered in which outcome measures obtained less than one year following diagnosis and initiation of treatment are grouped together with those measured in other subjects several years after therapy was instituted. Consequently, it is very difficult to compare the results of such studies. Another major problem is the wide variability of methods and criteria for assessing outcome. While most studies have addressed

both seizure control and mental/developmental status as markers of outcome, there is no standard for quantifying such measures. For example, definitions of normality vary greatly among reported studies, even when standardized testing protocols are employed, as do the exact criteria for determining mild, moderate and severe degrees of mental retardation/developmental delay. Consequently, when summarizing the results of many studies it has been necessary to use relatively broad groupings of most outcome measures, and to provide ranges of most reported measures rather than to attempt a more quantitative synthesis.

In an attempt to derive meaningful overall outcome measures, we have focused on a subset of published reports, including 67 studies (see Appendix 3) which included at least 25 subjects each (range 25-466, mean = 85), and in which the patient population was not preselected (i.e., studies were not included if they were restricted to only cryptogenic, or only symptomatic patients, or other specific etiological categories, or if patients were preselected in any manner with respect to treatment response or other outcome measures). The minimum follow-up period averaged 31 months in the 52 studies which provided specific information, although there was a very wide range, with occasional patients being re-evaluated within a month, and others after more than 30 years. Other studies, including specifically selected populations and smaller numbers of subjects, have been subsequently analyzed in order to assess the influence or predictive value of various factors with respect to long-term outcome.

2. MORTALITY

2.1 Overall outcome

In this section, studies of mortality are considered as a group, without regard to the influence of specific etiological factors or the type of therapy used. In the next section, the various factors that may influence the death rate are considered. The subset of studies described above, and specified in Appendix 3, includes 34 reports in which mortality was assessed. These studies are summarized in Fig. 12.1, which plots the reported death rate (the percentage of the total study population determined to have died prior to the follow-up date) for each of the reports versus the year of publication. Since follow-up periods within these studies were typically more than 3 years, and often much longer, the date of publication does not reflect the actual year in which deaths occurred, but does provide an upper limit.

As reflected in Fig. 12.1, there is a wide range in the mortality figure, with individual studies reporting values ranging from zero to as high as 41%. The average value for all 34 studies was 12.1% (not corrected for the variable number of cases in the different studies). While the marked differences in the protocols of the individual studies, in particular, the highly variable follow-up periods, preclude a meaningful statistical analysis, the data in Fig. 12.1 do suggest that the mortality rate in this disorder has declined somewhat over the

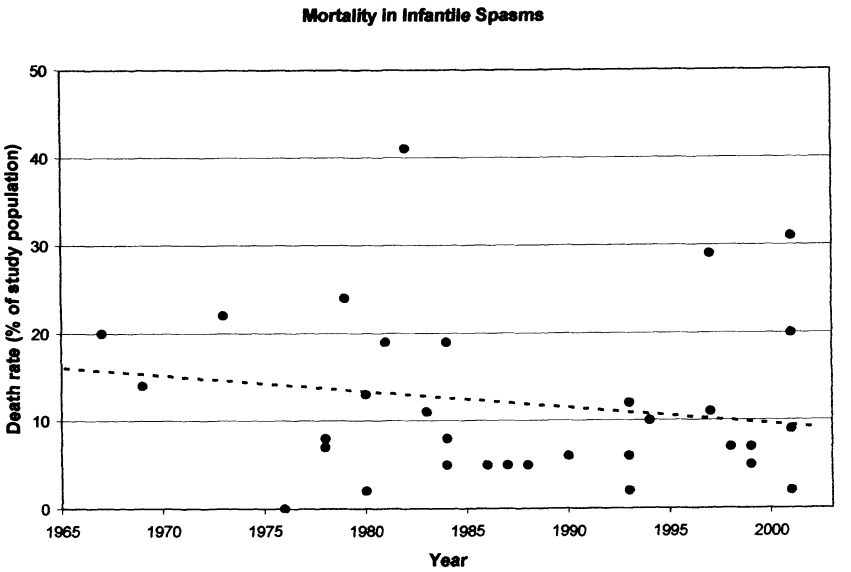

Figure 12.1 Reported death rates in 34 studies of infantile spasms. Values plotted by date of publication. Studies with fewer than 25 cases were not included. Studies were also excluded if the population was preselected by etiological, diagnostic or outcome variables. The dashed trendline displays the results of linear regression analysis, and suggests that death rates have decreased slightly over the past 35 years. References provided in Appendix 3, part 1.

past 35 years, from a typical value of around 15% prior to 1975 to approximately 10% in more recent years. Presumably this decrease reflects improved management of the various medical complications common in this disorder.

The reason for the wide variability of the death rates observed in these studies is not clear. To some extent it appears to reflect random variation within small groups, since the studies reporting both the lowest (0%; Seki et al., 1976) and highest (41%; Kurokawa et al., 1982) mortality values were based on relatively small populations (25 and 27 patients, respectively). However, random chance does not appear to be the only factor contributing to the variability since limiting the analysis to studies with populations exceeding 100 patients still reveals a mortality range of 2-31%. Consequently, it is likely that methodological differences between studies also contribute significantly to the observed variability. For example, among the 12 studies with group sizes exceeding 100 patients, the study reporting the lowest mortality rate (2%; Ito et al., 2001) and that reporting the highest rate (31%; Riikonen, 2001a) were similar in that both had a follow-up period of approximately 20-30 years, the majority of patients were treated with ACTH, and the percentages of cryptogenic patients were comparable. However, the former study, with the lowest reported death rate, was based entirely on a questionnaire sent to caregivers, and cases were included in the analysis only if the questionnaire was completed and

returned. The latter study, with the higher mortality value, was based on analysis of hospital records, supplemented with questionnaires to caregivers. In this study, the patients had all been participants in a prospective study conducted in the 1960s, and follow-up information was obtained in 100% of the cases. Thus, it is possible that the lower mortality values observed in the former study resulted from a selective response rate to the questionnaire, with parents of children who had died responding at a lower rate than parents of surviving children.

The causes of death in infantile spasm patients are also varied, although most studies have not provided specific information regarding this subject. In the study by Kurokawa et al. (1982) which reported an overall mortality of 41%, 10 of the 11 deaths occurred in children who were severely mentally retarded. Specific causes included pneumonia (36%), emaciation (18%), suffocation (18%), and seizures (9%). Riikonen (2001a) reported a death rate of 31% in a population of 214 patients, and noted that all but one of these children were mentally retarded. Infection was the most common immediate cause of death, and 8 patients died during ACTH therapy (all demonstrated adrenal enlargement and hypertrophic cardiomyopathy).

2.2 Predictive factors

Cryptogenic versus symptomatic In most studies, the death rate in children who fall into the cryptogenic diagnostic category at the onset of spasms (i.e., absence of apparent etiological factors, prior normal development, and normal CT/MRI studies) has been found to be significantly lower than that reported in symptomatic patients. In 11 studies which investigated this relationship, the average percentage of patients in the cryptogenic category who had died by the time of follow-up was 3% (range 0-18%), as compared to an average rate of 14% (range 0-37%) for the symptomatic group (Jeavons et al., 1973; Seki et al., 1976; Chevrie and Aicardi, 1978; Matsumoto et al., 1981c; Cavazutti et al., 1984; Fois et al., 1984; Glaze et al., 1988; Guzzetta et al., 1993; Holden et al., 1997; Siemes et al., 1998; Battaglia et al., 1999).

Effect of treatment There is insufficient information available to determine if the various therapeutic modalities used in the management of infantile spasms have significant effects upon the observed death rate. In an early study, Jeavons et al. (1970) reported a death rate of 16% in a group of patients treated with ACTH or corticosteroids, which was slightly lower than the 29% rate observed in untreated subjects. However, in view of the relatively small number of subjects, it is unlikely that this difference was statistically significant. In a subsequent paper which included a larger number of subjects, this same group (Jeavons et al., 1973) reported that there was no significant difference in the death rate of patients treated with ACTH/corticosteroids in comparison to those treated with other agents, or untreated. Similar results were also reported by Friedman and Pampiglione (1971). Thus, while serious side effects may occur

during ACTH/corticosteroid therapy (Chapter 11, section 2.1.7), this factor may not significantly impact the overall death rate. This possibility is supported by the study of Riikonen (2001a) cited above (section 2.1). While 8 patients in this study died while receiving ACTH, these patients accounted for only 12% of the total deaths that occurred in the study. Holden et al. (1997) found no differences in the death rates of patients with very short treatment lags (<30 days), as compared to those with treatment delays exceeding 30 days. Similarly, no significant difference in mortality was noted in patients receiving high-dose ACTH therapy, as compared to those receiving low-dose therapy (Chadwick et al., 2001). There is insufficient information available to determine if the mortality rate is different in patients who show an initial favorable response to therapy (i.e., cessation of spasms) in comparison to nonresponders.

Age of onset Chevrie and Aicardi (1978) reported that the death rate was significantly higher (11%) in the group of patients that had onset of spasms within the first 6 months of life, as compared to patients with a later onset (death rate 3%).

3. MENTAL OUTCOME/ACHIEVEMENT LEVEL

3.1 Overall prognosis

The overall probability of achieving normal mental development following a diagnosis of infantile spasms is low. The average value for the 50 studies with unselected populations (summarized in Appendix 3) was 16%, with a range of 0% to 35%. The reported percentages of patients found to have a normal mental/developmental outcome in these studies are plotted versus the date of publication in Fig. 12.2, illustrating the relatively wide variability of this measure across studies. Fig. 12.2 also demonstrates that the likelihood of a favorable outcome has increased only slightly over the years, from a typical value of around 12-13% in the 1960s, to approximately 16-18% in recent years.

The variability in the percentage of patients attaining a normal mental outcome appears to be in part a result of chance factors related to study size. The study reporting the best outcome (Haginoya et al., 2000; 35% normal), and that with the worst (Trojaborg and Plum, 1960; 0% normal) were both relatively small (26 and 30 subjects, respectively). When only studies with more than 100 subjects are considered, the variability is somewhat smaller, ranging from 3% to 25%, but still broad enough to suggest that other factors related to experimental design may have been influential.

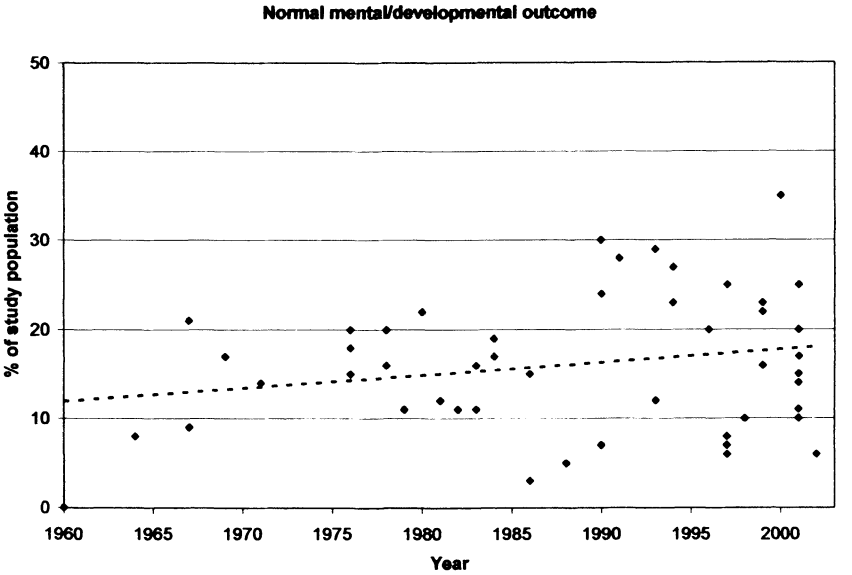

Figure 12.2 Reported percentage of patients with a normal mental/developmental outcome in 50 studies of infantile spasms. Values plotted by date of publication. Studies with fewer than 25 cases were not included. Studies were also excluded if the population was preselected by etiological, diagnostic or outcome variables. The dashed trendline displays the results of linear regression analysis, and suggests that the chances for normal mental development have increased only slightly over the past 35 years. References provided in Appendix 3, part 1.

3.2 Influence of treatment

3.2.1 Medical therapy

While one of the primary goals of treatment of infantile spasms is improvement of mental/developmental outcome, there is, at present, no conclusive evidence that any of the therapeutic modalities used in this disorder actually provide this benefit. As reviewed in the previous chapter (Chapter 11), a number of treatment options are available, and some of these modalities are effective in terms of seizure control, often leading to complete cessation of spasms in a significant fraction of the patient population. For this reason, patients with infantile spasms are almost universally treated, and so, for ethical reasons, it has become very difficult, if not impossible, to devise statistically relevant studies capable of determining any independent effect of the treatment on mental development. Thus, there have been no placebo controlled long-term studies of any of the available therapeutic approaches, and only a few early studies included untreated subjects. As reviewed below, the best information currently available is indirect, and is derived mainly from comparative studies of two or more different therapies, as well as evaluation of outcomes in subjects

who achieve seizure control following initiation of treatment, in comparison to those who do not respond. Such experimental designs have not provided definitive answers for a number of reasons, including multiple factors influencing selection of the initial drug, and the fact that many patients do not respond to the initial drug, and so may be treated with multiple agents. Such factors, coupled with the small sample sizes of most studies due to the relative rarity of this disorder, have, so far, prevented any quantitative resolution of the question of long-term therapeutic benefit.

Following the initial reports documenting the effectiveness of ACTH in controlling the spasms and improving the EEG characteristics in some patients with infantile spasms (Sorel and Dusaucy-Bauloye, 1958; Low, 1958), several studies addressed the potential long-term benefits of this novel therapy on mental development by comparing the outcomes of subjects treated with ACTH or corticosteroids to those of other groups that had either received no treatment, or had received medications commonly in use at that time, but which were thought to be ineffective. For example, Jeavons et al. (1970, 1973) found no significant difference in mental outcome (as assessed by educational status) after follow-up periods of 2-12 years for patients treated with ACTH or corticosteroids, as compared to those patients who were untreated or received other agents (including chlortetracycline, pyridoxine, and various anticonvulsants). Similar conclusions were reached by Friedman and Pampiglione (1971) who assessed both IQ and educational ability after 6-12 years, and by Mizutani (1969) who assessed IQ after 5-17 years, with both studies finding no evidence for a superior effect of ACTH/corticosteroid therapy. Gibbs and Gibbs (1976) also found no overall superiority of ACTH, but did report that severe mental retardation was less frequent in the ACTH-treated cryptogenic patients (15% of 129 subjects) than in cryptogenic patients not receiving ACTH (44% of 87 subjects). The statistical significance of this finding was not presented, and there was little difference in the percentages of patients with normal intelligence at follow-up (21% for ACTH treated and 16% for the controls). In our own retrospective study (Hrachovy et al., 1991) comparing 44 patients not treated with hormonal drugs (prior to 1960) with a group of 38 subjects receiving ACTH or prednisone more recently (Glaze et al., 1988), there was no statistically significant difference between the two groups with respect to developmental outcomes. Only one study of this type (Snyder, 1967) reported an apparent benefit of corticosteroid therapy, with 29% of 28 patients showing normal development at follow-up, compared to 10% of the 20 subjects who received other forms of treatment (no statistical analysis was provided).

In a study that compared groups receiving very high doses of ACTH (150u/m^2/day) and more conventional doses (20-30 u/day), there was no significant difference in developmental outcome between the two groups at an average follow-up time of 10 years (Chadwick et al., 2001). However, in a somewhat similar study (Ito et al., 1990) which evaluated the relative effectiveness of very low doses of ACTH (0.01-0.5mg/kg/day; approximately

equivalent to 0.4-20u/kg/day), patients receiving doses greater than 0.04 mg/kg/day had a better outcome (88% normal or only mildly retarded), as compared to subjects receiving lower doses (33% normal or only mildly retarded). While this finding was statistically significant, the number of subjects in the two groups was small (8 and 21, respectively, and the findings are difficult to reconcile with the studies noted in the preceding paragraph.

There have been very few studies in which ACTH/corticosteroid therapy was directly compared to other modalities with respect to long-term mental outcome. In one small series (28 subjects) there was no difference in outcome between subjects treated with ACTH and those receiving valproic acid (Holden et al., 1997). Similarly, no difference in cognitive outcome was observed between a group of symptomatic patients treated with ACTH, and a comparison group treated with nitrazepam (Koo et al., 1993).

A possible enhanced efficacy using a combination of high-dose pyridoxine and low-dose ACTH therapy has been suggested by Takuma (1998), who reported a normal mental outcome in 48% of 21 patients. While this result is considerably higher than the average value of approximately 16% reported in other studies (see Section 3.1), the small size of the study makes it difficult to assess the significance.

Considering the above findings, it must be concluded that even though ACTH and corticosteroids, and some other medications, have been shown to be efficacious in terms of initial spasm control and improvement of EEG characteristics, a long-term benefit in terms of improved mental development has not been proven.

3.2.2 Surgical therapy

The possibility that focal resective surgery may be a useful therapy for intractable infantile spasms (Chugani et al., 1990) has generated considerable interest in recent years (Chapter 11, section 3.2). While there have, as yet, been no prospective comparative studies evaluating outcome in patients treated surgically with control groups treated medically, several studies have provided preliminary information regarding potential long-term benefits. For example, in a study by Chugani et al. (1993), 7 of 23 patients were followed for 3 years or longer (36-67 months), and 6 of the 7 (86%) were determined to have significant mental/developmental delay. Asarnow et al. (1997) evaluated 24 surgically treated patients approximately 2 years post-surgery, and found that while most remained significantly impaired (4% normal, based upon the Vineland Adaptive Behavior Scale [VABS]), there had been a significant increase of the VABS scores compared to presurgical levels. They also compared their findings to the outcome of Riikonen's previously published (1982) series, and concluded that the surgical group had a somewhat more favorable outcome. Caplan et al. (1999, 2002) evaluated the development of non-verbal communication using the Early Social Communication Scale (ESCS) in a group of medically refractory patients

who subsequently had resective surgery (typically either hemispherectomy or multilobar resection). They found that at approximately 2 years following surgery there was a significant increase of social interaction, although, overall, most children remained below the normal range with respect to the ESCS measures.

3.2.3 Treatment lag

Another aspect of therapy that has generated a considerable degree of controversy is the relationship between treatment lag (i.e., the elapsed time between onset of the disorder and institution of treatment) and cognitive outcome. This topic has considerable theoretical, as well as practical implications. If it could be established that early treatment results in a significant improvement in long-term mental development as compared to delayed therapy, this would provide indirect evidence that medical treatment actually does influence the progression of the disorder beyond that of simple seizure control. Unfortunately, as with so many other aspects of this disorder, the available evidence is conflicting and does not permit a definitive assessment of this possibility.

Several studies have reported a positive correlation between a treatment lag less than 1-3 months and favorable mental outcome. For example, Koo et al. (1993) found that mental development was normal, or only mildly delayed, in 50% of cryptogenic patients treated within a month of onset (ACTH or nitrazepam), as compared to 36% of those patients whose therapy was delayed more than 30 days. Similarly, 23% of symptomatic subjects treated within 30 days had a favorable outcome, compared to only 14% of those with treatment lags exceeding 30 days. The findings were statistically significant for both the cryptogenic and symptomatic groups. Several other studies have reported similar results in mixed groups of cryptogenic and symptomatic subjects, although data for the two groups were not analyzed separately (Chevrie and Aicardi, 1971; Ohtahara et al., 1976; Ferraz et al., 1986; Riikonen, 1996b). A few investigators have reported improved mental outcome only in cryptogenic patients with short treatment lags, but apparently did not assess this factor in their symptomatic subjects (Snyder, 1967; Sakuma et al., 1980; Lombroso, 1983). On the other hand, in two additional studies which, like Koo et al. (1993), did examine both cryptogenic and symptomatic patients, a positive correlation with improved mental development was found only in the cryptogenic groups (Matsumoto et al., 1981b,c; Fois et al., 1984). Finally, there have been a number of reports in which the investigators did not find a relationship between treatment lag and improved mental outcome (Glaze et al., 1988; Wang et al., 1994; Holden et al., 1997; Wong, 2001; Young, 2001; Ito et al., 2002). Most of these studies provide relatively few details of these negative findings, or of the differences found between cryptogenic and symptomatic groups. In one study of 64 subjects that did report such information, a somewhat

higher percentage of cryptogenic patients with treatment lags <5 weeks (40%) had favorable outcomes compared with those whose treatment lag was >5 weeks (33%), but these results were not statistically significant (Glaze et al., 1988).

In reviewing the above studies, no specific reasons for the discrepant results could be determined. In general, the studies reporting a positive correlation between treatment lag and mental outcome, both across all patients and those restricted to cryptogenic subjects only, tended to be larger (the average number of subjects was 124, as compared to an average value of 60 subjects for the negative studies), and to contain a higher percentage of cryptogenic subjects (average value of 34% for the positive studies, and 22% for the negative studies). However, other factors such as experimental design, follow-up periods, and medications evaluated appeared to be generally comparable. Consequently, the exact influence of treatment lag in this disorder is, at present, unclear. If there is an effect, it may be restricted primarily to cryptogenic subjects.

3.3 Predictive factors

Cryptogenic versus symptomatic The factor most predictive of a favorable outcome with respect to mental development is classification as cryptogenic at the time of initial diagnosis. An analysis of 20 studies which addressed this relationship revealed that an average of 51% of the cryptogenic patients achieved a normal mental status by the time of the follow-up evaluation, with a range of 19-100% observed in the individual reports (Snyder, 1967; Chevrie and Aicardi, 1971; Gibbs and Gibbs, 1976; Ohtahara et al., 1976; Chevrie and Aicardi, 1978; Matsumoto et al., 1981a,b,c; Lombroso, 1983; Fois et al., 1984; Cavazutti et al., 1984; Glaze et al., 1988; Prats et al., 1991; Vacca et al., 1992; Heiskala et al., 1996; Riikonen, 1996b; Iinuma, 1999; Rantala and Putkonen, 1999; Battaglia et al., 1999; Ohtsuka et al., 2000; Sugai et al., 2001; Young, 2001). Conversely, the average value for normal mental development was only 6% of those patients classified as symptomatic, with a range of 0-41% in the individual studies. Etiological factors associated with particularly unfavorable outcomes include intraventricular hemorrhage, asphyxia, congenital anomalies, chromosomal anomalies and meningitis (Glaze et al., 1988) and infections of all types (Riikonen, 1993). However, classification as cryptogenic does not ensure a favorable outcome, and in the average study 23% of these patients were determined to have severe mental retardation at follow-up, with a range of 0-47% in 12 studies which examined this aspect (Chevrie and Aicardi, 1971; Gibbs and Gibbs, 1976; Chevrie and Aicardi, 1978; Matsumoto et al,. 1981c; Cavazutti et al., 1984; Favata et al., 1987; Glaze et al., 1988; Koo et al., 1993; Battaglia et al., 1999; Ohtsuka et al., 2000; Sugai et al., 2001; Young, 2001). Severe mental retardation is much more common in symptomatic patients, with an average value of 65% (range 29-91%) in 11 studies that were reviewed (Chevrie and Aicardi, 1971; Chevrie and Aicardi, 1978; Matsumoto et al., 1981c; Cavazutti et al., 1984; Favata et al., 1987; Glaze et al., 1988; Koo et al.,

1993; Battaglia et al., 1999; Ohtsuka et al., 2000; Sugai et al., 2001; Young, 2001).

Several reports have also documented the correlation of abnormal brain imaging studies with an unfavorable outcome (Matsumoto et al., 1981b; Curatolo et al., 1986; Favata et al., 1987; Takahashi et al., 1990; Okumura et al., 1998).

Initial developmental status Many investigators have identified the mental/developmental status at the time of diagnosis as a useful predictive factor, with favorable long-term outcome observed more frequently in those patients with normal status documented at the initial examination (Mizutani, 1969; Jeavons et al., 1973; Seki et al., 1976; Sakuma et al., 1980; Matsumoto et al., 1981b; Wasser et al., 1983; Favata et al., 1987; Glaze et al., 1988; Czochanska et al., 1994; Wang et al., 1994; Battaglia et al., 1999; Matsuo et al., 2001a,b; Riikonen 2001a). However, this is not surprising in view of the data reviewed in the preceding paragraph, since a patient with abnormal development prior to the onset of infantile spasms would necessarily also be classified as symptomatic. Thus, the crucial issue is whether or not mental status at diagnosis is actually an independent predictive factor, and this has not yet been determined. The only statistically significant data suggesting that this factor may also provide useful predictive information independent of that provided by the symptomatic category was provided in the study by Curatolo et al., (1986), in which stepwise discriminant analysis was used to identify the most useful variables. However, this study did not independently assess a group of patients in the conventional symptomatic category to determine the additional and independent predictive power of the initial mental status determination.

In considering the significance of the mental/developmental status at the time of initial diagnosis, it is critical to differentiate between patients whose status was abnormal prior to onset of infantile spasms, and continues to be abnormal, and those patients whose development was normal up to the time of spasm onset, but has declined since that time. The prognosis in the former patients is clearly poor, as they fall into the symptomatic category, but can be favorable in the case of patients in the latter category. In a study of 15 cryptogenic patients (Gaily et al., 1999), all of whom had normal development prior to onset of spasms, it was demonstrated that 10 subjects (67%) exhibited some degree of developmental delay when tested after the onset of spasms. The outcome in this group of 15 patients was generally good, with 80% having a normal IQ at 4-6 years of age. Additionally, there was no significant difference in the ultimate outcomes of the 10 children who had transient developmental delays after spasm onset, in comparison to those who maintained normal developmental milestones throughout their course. Similar findings were reported by Guzzetta et al., (1993), who reported that mild developmental delay (DQ>60) occurred following spasm onset in 5 subjects with previously normal development, but that all were mentally normal at the final evaluation 2.3 to 5.0 years later.

Initial response to therapy A number of studies have examined the predictive value of the initial response to therapy with respect to long-term cognitive development, and in some, a positive correlation was found between initial seizure control and a favorable mental outcome. For example, in the study by Riikonen (1996b) which included 214 subjects, 70% of the cryptogenic patients whose spasms were controlled by ACTH therapy had a favorable outcome (normal or only mildly impaired), as compared to only 20% of the subjects who did not respond to the initial treatment. Symptomatic patients exhibited a similar, but less pronounced, pattern with 23% of the responders proving to have a favorable outcome, whereas all of the nonresponders were in the moderate or severely retarded categories. A number of other studies, which included treatment with several agents in addition to ACTH, have reported similar findings (Matsumoto et al., 1981b; Koo et al., 1993; Wohlrab et al., 1998). However, several other studies which examined this relationship found no evidence of a significant correlation between mental outcome and the initial response to therapy (Bray, 1963; Favata et al., 1987; Glaze et al, 1988; Ito et al., 2002).

Relapse The occurrence of a relapse following an initial favorable response to therapy has been correlated with a less favorable cognitive outcome in several studies (Tsuchiya and Fukuyama, 1978; Matsumoto et al., 1981c [cryptogenic cases only]; Glaze et al., 1988; Matsuo et al., 2001a,b). For example, in the studies by Matsuo et al. (2001a,b), the average developmental quotient at follow-up was significantly lower in 24 patients who relapsed after an initial response to therapy in comparison to that observed in 14 patients whose spasms did not recur (DQ of 15 in the patients with relapse and 44 in the group with sustained control). However, in two other studies no correlation was found between the occurrence of a relapse and mental outcome (Riikonen, 1982; Wang et al., 1994).

Presence of SPECT/PET abnormalities Several recent studies have investigated the relationship between functional abnormalities identified by PET/SPECT and long-term mental outcome. In a study of 26 patients, including 10 cryptogenic and 16 symptomatic patients, no correlation was found between the presence of focal cortical lesions identified by SPECT near the time of diagnosis, and mental/developmental status more than two years later, in comparison to patients who had normal imaging studies (Haginoya et al., 2000). Similarly, in a study of 17 cryptogenic subjects using PET imaging (Itomi et al., 2002), no difference in developmental outcome was identified in patients exhibiting focal hypometabolic areas prior to institution of therapy, as compared to those with normal PET findings. However, in this latter study it was determined that an abnormal PET examination 3 months after institution of treatment was associated with a poor developmental prognosis since nine (75%) of 12 children with normal PET studies had normal development, while all 5 of those with focal hypometabolism were delayed. Chugani et al. (1996) reported that patients with medically refractory infantile spasms who had bilateral temporal hypometabolism, and thus were not candidates for surgery, had a very

poor long-term prognosis. All 14 of their patients with this condition had significant developmental delay with minimal or absent language development, and 10 (71%) were autistic.

Tuberous sclerosis There is general agreement that the presence of both tuberous sclerosis and infantile spasms is a very unfavorable prognostic indicator, and few patients (0-16% in the reviewed studies) with this diagnostic complex are found to have normal mental development at follow-up (Fois et al., 1984; Yamamoto et al., 1987; Glaze et al., 1988; Riikonen and Simell, 1990; Jozwiak et al, 1998).

Other seizures In a number of studies the occurrence of other seizure types (in addition to spasms), either before the onset of infantile spasms, concurrently with spasms, or later, after spasms have ceased, has been found to be an unfavorable prognostic sign, with such patients being less likely to achieve normal mental development (Tsuchiya and Fukuyama, 1978; Riikonen and Amnell, 1981; Riikonen, 1982; Lombroso, 1983; Koo et al., 1993; Haga et al., 1995a). However, this may not be an independent factor, since it is also known that symptomatic patients are more likely to have other seizure types than children in the cryptogenic category (Riikonen and Simell, 1990; Koo et al., 1993; Lortie et al., 1997). In addition, not all studies have found a significant relationship between other seizure types and prognosis for an unfavorable mental outcome (Chevrie and Aicardi, 1971; Wang et al, 1994).

Age at onset of infantile spasms A relationship between the age of onset of spasms and long-term mental development has been reported by a number of investigators. As one example, Chevrie and Aicardi (1978) reported that 30% of children whose spasms began after 6 months had a normal mental status at follow-up (1-7 years), while only 14% of those whose seizures began within 6 months of birth had a normal outcome. A similar correlation between early onset (typically < 3-7 months) and poor outcome has been observed in several other studies (Jeavons et al., 1973; Seki et al., 1976; Sakuma et al., 1980; Wasser et al., 1983; Ferraz et al., 1986; Sher and Sheikh, 1993; Wang et al., 1994). However, this particular correlation has not been observed in many other studies which evaluated the relationship between onset age and long-term prognosis (Ohtahara et al., 1976; Matsumoto et al., 1981c; Favata et al., 1987; Glaze et al., 1988; Madge et al., 1993; Stafstrom and Konkol, 1994; Riikonen, 1996b; Battaglia et al., 1999; Gaily et al., 1999; Wong, 2001; Ito et al., 2002).

EEG characteristics at diagnosis and following therapy The occurrence of a typical hypsarrhythmic pattern at the time of diagnosis, as opposed to a variant, atypical or asymmetric pattern, has been found to be a favorable prognostic indicator by several investigators (Ohtahara et al., 1976; Lombroso, 1983; Vacca et al., 1992). Lombroso (1983), for example, found that 37% of 133 patients with typical hypsarrhythmia had normal outcomes, in contrast to 20% of 66 children with atypical patterns. Similar findings were reported by Vacca et al. (1992), with 27% of patients with a typical hypsarrhythmia showing a complete recovery at follow-up (>8 months), in comparison to 11% of those with atypical

hypsarrhythmic patterns. Kramer et al. (1997b) calculated a severity score for each EEG, based upon multiple features (e.g., disorganization, voltage, amount of slow activity, frequency of spike/sharp wave activity, etc.) and demonstrated that favorable outcome correlated with lower scores on this measure. Failure of EEG normalization after institution of ACTH therapy has also been identified as a predictor of poor outcome in two studies (Harris, 1964; Tsuchiya and Fukuyama, 1978).

On the other hand, in a study of 17 patients with tuberous sclerosis and infantile spasms, Husain et al. (2000) found no significant differences in the EEG characteristics, awake and asleep, of those patients who had a good response to therapy and those who did not. In several other studies the investigators have failed to find any correlation between various EEG features and long-term outcome (Jeavons et al., 1973; Riikonen, 1982; Koo et al., 1993; Gaily et al., 1999).

In general, asymmetrical EEG patterns are associated with a less favorable outcome due to the association with underlying structural abnormalities of the brain (see above). Dulac et al. (1993a) reported that an asymmetrical hypsarrhythmia is also an unfavorable prognostic indicator in cryptogenic patients, with 13 of 15 (87%) patients (from a total group of 45 infants with a cryptogenic classification) who exhibited such a pattern having an unfavorable outcome.

Dulac et al. (1986b, 1993a) have proposed that the occurrence of hypsarrhythmia between individual spasms in a cluster ("independent" spasms) is a favorable prognostic indicator, in contrast to "non-independent" spasms, characterized by an absence of the hypsarrhythmic pattern between individual spasms. In their 1993 study, which included 28 cryptogenic patients with spasm clusters, 94% of the 16 subjects who had normal mental development and good seizure control had independent spasms, while only 25% of the 12 patients with abnormal mental outcomes and/or continuing seizures exhibited this pattern. Fusco and Vigevano (1993) reported similar findings with 80% of their cryptogenic patients exhibiting the independent pattern, as compared to 30% of the symptomatic group. Additional evidence in support of this relationship was provided by Plouin et al. (1987, 1993). However, Haga et al. (1995a) were unable to confirm this relationship, and found that only one (14%) of 7 cryptogenic patients with favorable outcomes had the independent pattern. In addition, Silva et al. (1996) found that independent spasms occurred in all 7 of the Down syndrome cases in which they were able to record clusters of spasms. Watanabe et al. (2001) has also questioned the significance of independent spasms, and reported that during clusters that exhibit a waxing and subsequent waning of intensity, interspasm hypsarrhythmia may be present at the beginning and end of the series, when the intensity is low, but disappear during the midportion of the cluster when spasms are most intense.

Miscellaneous factors Family history of epilepsy has been examined by several investigators as a possible predictive factor, but the findings are variable.

For example, Battaglia et al. (1999) found that 55% of patients with a negative family history had a normal IQ at follow-up, whereas only 14% of the group with a positive family history had normal development. However, no correlation of outcome and family history was observed in two other studies (Chevrie and Aicardi, 1978; Wong, 2001).

It has been reported that the prognosis for a favorable cognitive outcome is improved in patients whose spasms cease within 4-10 months, as compared to those whose spasms persist for longer periods of time (Jeavons et al., 1973; Seki et al., 1976).

4. SEIZURE CONTROL

4.1 Persistence of spasms and/or other seizure types

Epileptic spasms typically cease within several years, and are rare in older children and adults. In several studies in which patients with infantile spasms were followed for at least 2-5 years, spasms were reported to be continuing at the time of follow-up in only 1-12% (average 7%) of the subjects (Livingston et al., 1958; Jeavons et al., 1973; Riikonen and Amnell, 1981; Yamamoto et al, 1987). When spasms do persist beyond the second year, other seizure types are common, and most patients exhibit severe cognitive impairment (Sotero de Menezes and Rho, 2002). However, infantile spasms patients frequently develop other types of seizures whether or not spasms continue, and these often persist indefinitely. Information regarding the presence or absence of seizures at the time of follow-up was provided in 44 of the studies included in Appendix 3, and the individual values (percentage of total population with uncontrolled seizures) are plotted versus study publication date in Fig. 12.3. The values listed in Appendix 3 in most cases reflect the number of patients still experiencing seizures of any type (including epileptic spasms) at the time of the follow-up evaluation. However, in some instances it could not be determined from the information provided how many patients, if any, were still experiencing spasms at that time, and whether or not they were included in the overall figure. In several other studies, separate values were provided for the number of patients with continuing spasms, but it was not clear if some or all of these subjects were also included in the category for other seizure types. Consequently, in such instances, we have used the most conservative (i.e., lowest) value consistent with the data provided. On average, 51% of these subjects continued to experience seizures at the time of the follow-up evaluation, although there was a great deal of variability across studies (range 9% to 86%). Inspection of the trend indication in Fig. 12.3 also suggests that the fraction of patients with uncontrolled seizures has not changed significantly over the past 35 years.

The reasons for the extreme degree of variability observed for this parameter are not clear. Sample size does not appear to be the major factor, since the variability observed in 33 studies with 100 or fewer patients (range 9% to 84%)

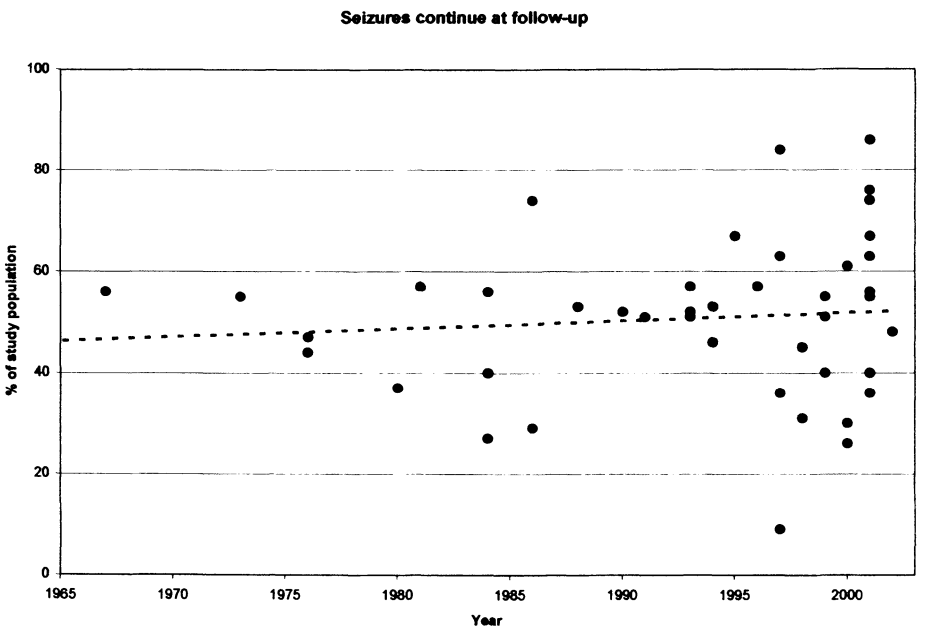

Figure 12.3 Reported percentage of patients with uncontrolled seizures (of any type) at the time of follow-up. Values plotted by date of publication. Studies with fewer than 25 cases were not included. Studies were also excluded if the population was preselected by etiological, diagnostic or outcome variables. The dashed trendline displays the results of linear regression analysis, and suggests that the fraction of patients whose seizures can not be controlled has not changed significantly over the past 35 years. References provided in Appendix 3, part 2.

is similar to that observed in the 11 studies with more than 100 subjects (range 27% to 86%). Consequently, it is likely that differences in experimental design account for at least some of the observed variability. One such factor could be the wide range of elapsed time between the initial and follow-up evaluations in these populations, both within and across studies (see Section 1, above).

4.2 Predictive factors

Cryptogenic versus symptomatic Patients classified as cryptogenic at the time of initial diagnosis are much less likely to have uncontrolled seizures of any type at the time of follow-up. In 15 studies which provided information concerning this relationship, seizures were continuing in an average of 23% of the cryptogenic patients (range of 0-46% in the individual studies), as compared to 54% (range 24-75%) of the symptomatic group (Jeavons et al., 1973; Gibbs and Gibbs, 1976; Lombroso, 1983; Cavazutti et al., 1984; Suzuki et al., 1986; Prats et al., 1991; Vacca et al., 1992; Koo et al., 1993; Heiskala et al., 1996; Battaglia et al., 1999; Iinuma, 1999; Fejerman et al., 2000; Ohtsuka et al., 2000; Sugai et al., 2001; Ito et al., 2002). Okumura et al. (1998) evaluated the

correlations between seizure status and initial MRI findings in a group of 77 patients with infantile spasms. They found that a normal MRI was associated with a later onset of infantile spasms, an earlier cessation of spasms, and a lower incidence of subsequent seizures of any type.

Effect of treatment Treatment with ACTH or corticosteroids, while sometimes effective for the initial control of spasms, does not appear to increase the chances that a patient will be seizure-free over the longer term. Several of the earlier studies that compared groups receiving hormonal therapy to others receiving conventional anticonvulsant therapy found no significant differences between groups with respect to the percentage of subjects who were seizure-free at the final evaluation (Snyder, 1967; Jeavons et al., 1970; Gibbs and Gibbs, 1976). Similarly, no significant differences in the number of seizure-free patients at follow-up were observed in two studies which compared various ACTH dose levels (Ito et al., 1990; Chadwick et al., 2001), or in a study comparing ACTH and valproate therapy (Holden et al., 1997). No difference in seizure outcome was observed between a group of symptomatic patients treated with ACTH, and a comparison group treated with nitrazepam (Koo et al., 1993).

Several studies (Curatolo et al., 1986; Wang et al., 1994; Wohlrab et al., 1998; Ohtsuka et al., 2000; Ito et al., 2002) have reported that the initial response to therapy (with several drugs) has predictive value with respect to long-term seizure control. For example, Wang et al. (1994) found that 75% of the patients whose spasms were controlled by initial therapy were seizure free at follow-up, as compared to an overall seizure-free rate of 47% for the entire group. On the other hand, two studies which also examined this relationship did not find a statistically significant relationship (Matsumoto et al., 1981b; Glaze et al., 1988).

Treatment lag Several investigators have noted a relationship between treatment lag and seizure control, reporting that patients treated within 1-3 months of spasm onset are less likely to have continuing seizures than are those patients with longer delays (Matsumoto et al., 1981b [cryptogenic only]; Lombroso, 1983 [cryptogenic only]; Ito et al., 2002). However, this relationship between treatment lag and seizure control was not found in all studies (Koo et al., 1993; Holden et al., 1997). Matsumoto et al. (1981c) observed that children in the cryptogenic category who relapsed, with return of spasms following an initial favorable response to therapy, were more likely to have continuing seizures at the time of long-term follow-up than were patients who had a sustained initial response to treatment.

Age of onset The age of onset of infantile spasms has been found to correlate with seizure outcome in several studies (Jeavons et al., 1973; Curatolo et al., 1986; Madge et al., 1993; Ito et al., 2002), with an earlier onset (typically <3-4 months) being associated with a higher probability of uncontrolled seizures at follow-up. A similar trend was noted by Battaglia et al. (1999), but the results were not statistically significant.

EEG characteristics at diagnosis and following therapy As with cognitive outcome, the occurrence of a typical hypsarrhythmic pattern at the time of

diagnosis, as opposed to a variant, atypical or asymmetric pattern, has been found to be a favorable prognostic indicator in terms of seizure control (Ohtahara et al., 1976; Vacca et al., 1992).

Presence of SPECT/PET abnormalities Goto et al. (1999), in a study of 19 newly diagnosed infantile spasms patients, reported that patients who had abnormal SPECT findings (cerebral blood flow abnormalities) were more likely to achieve complete cessation of spasms (67% of those with corresponding MRI/CT lesions, and 83% of those with normal MRI/CT) with treatment than were those patients with normal perfusion studies (29%). However, the number of patients in this study was small, and the findings were not statistically significant.

5. PERSISTENCE OF EEG ABNORMALITIES

Of the 67 studies reviewed in Appendix 3, only 7 provided definitive information regarding EEG status at the time of follow-up. In these studies, the occurrence of EEG abnormalities ranged from as low as 23% of the patients to as high as 92%, with an average value of 61%. No reasons for the wide degree of variability of this measure were evident.

6. EVOLUTION TO LENNOX-GASTAUT SYNDROME

6.1 Frequency of occurrence

It has long been recognized that a significant number of patients with infantile spasms exhibit an evolution to the Lennox-Gastaut syndrome. Information regarding this transition was provided in 15 of the studies listed in Appendix 3, with an average of 17% of the patients diagnosed with Lennox-Gastaut syndrome at the time of follow-up. As with other parameters, this measure varied widely across studies. The highest rate (54% of the study population) was reported by Ohtahara et al. (1976) in a group of 94 patients, while no cases of Lennox-Gastaut syndrome were observed in a study by Iinuma (1999) in a study including 43 patients with infantile spasms. It seems likely that this variability is related to differences in study design, and, in particular, to the inconsistent follow-up periods.

6.2 Predictive factors and effect of therapy

In a prospective study including 42 patients treated with valproate (Prats et al., 1991) only 1 of 12 (8%) cryptogenic subjects exhibited an evolution to the Lennox-Gastaut syndrome, as compared to 7 of 27 (26%) symptomatic patients. A similar relationship was documented in a retrospective study of 37 subjects (Rantala and Putkonen, 1999) in which none of the 7 cryptogenic patients

developed characteristics of the Lennox-Gastaut syndrome, whereas 10 of 30 (33%) patients in the symptomatic category did develop this syndrome.

7. OTHER MEDICAL PROBLEMS

Many patients with infantile spasms, in particular those in the symptomatic category, have neurological deficits consistent with the underlying etiological factors. While this is generally recognized, relatively few studies have provided quantitative information regarding the long-term persistence of such deficits. Of the 67 studies included in Appendix 3, only 5 provided sufficient information to permit the frequency of significant neurological deficits at the time of follow-up to be determined. In these studies, the frequency ranged from a low value of 27% in a group of 165 subjects (Chevrie and Aicardi, 1978), to a high value of 60% in a population of 206 patients (Madge et al., 1993). The average value for these 5 studies was 44%. Several additional studies (not included in Appendix 3) have reported neurological abnormalities in 11-72% of the patients evaluated (Kellaway, 1959; Lombroso, 1983; Kurokawa et al., 1980; Nolte, 1988).

A relatively high incidence of psychiatric disorders has been reported. In a study of 192 patients, psychiatric problems were identified at follow-up (3-19 years) in 29%, and included autism (13%) as well as other categories (Riikonen and Amnell, 1981). Autistic-like behavior associated with infantile spasms was also noted by Delwarde et al. (1988), and in a high percentage (58%) of children with tuberous sclerosis and infantile spasms (Hunt and Dennis, 1987). Ichiba (1990) reported two cases with hyperlexia, characterized by the ability to read fluently, but with significantly impaired comprehension and autistic behavior. Chugani et al. (1996) found autistic behavior to be present in 73% of a group of patients with bilateral temporal hypometabolism who were refractory to medical therapy.

8. DISCUSSION AND SYNTHESIS

A summary of the overall prognosis for unselected infantile spasms cases is provided in Table 12.1, which is based on information from the studies reviewed in Appendix 3. Approximately 12% of the patients in these studies died prior to the follow-up evaluation, and only 16% had normal mental development. Approximately one half of the subjects (47%) had uncontrolled seizures at follow-up, and 17% had developed characteristics of the Lennox-Gastaut syndrome. Nearly half (44%) had persistent neurological deficits, and 61% had abnormal EEG findings.

However, the prognosis in this disorder is significantly altered by the presence of certain factors or diagnostic characteristics which may often be identified at the time of initial diagnosis. The most well-documented of these factors are presented in Table 12.2. Clearly, classification into the cryptogenic diagnostic category at the time of onset is the most favorable prognostic

***Table 12.1* Overall prognosis in infantile spasms**

(Estimates based on studies included in Appendix 3)

OUTCOME MEASURE	*FREQUENCY*
Death	**12%**
Normal mental development	**16%**
Continuing seizures	**47%**
Evolution to Lennox-Gastaut	**17%**
Abnormal EEG	**61%**
Persistent neurological deficit	**44%**

indicator, and significantly increases the probability of a normal developmental outcome. There is also some evidence that the three components of the cryptogenic categorization (normal prior development; normal imaging studies; and absence of etiological factors) may provide independent prognostic information as well, although this aspect has not been well-studied. Sustained response to therapy (without relapse), and absence of other seizure types are also considered to be favorable indicators. The final three factors listed in Table 12.2

Table 12.2
Factors associated with a favorable outcome

Cryptogenic diagnostic category

- **Normal mental/neurological development prior to onset**
- **Normal brain CT/MRI studies**
- **No known etiological factors**

Sustained response to therapy

Absence of seizure types other than spasms

Short treatment lag (?)

Age >6 months at onset (?)

Typical hypsarrhythmic pattern at onset (?)

(short treatment lag, older age of onset, and a classical hypsarrhythmic pattern) have also been identified in several studies as positive prognostic indicators, but the evidence is less convincing than with the other measures.

9. FUTURE RESEARCH

The most compelling need in this area is for well-controlled and prospective studies which provide various outcome measures at standardized time intervals following diagnosis, or at specific ages. The currently available information is difficult to interpret in a quantitative and statistically significant manner primarily because of the highly variable follow-up intervals in most of the studies, and the tendency to group the results of patients followed for relatively short periods of time (e.g, several months to a few years) with those followed for many years. There is also a need for more well-defined criteria for evaluating mental status, both at the time of diagnosis, and at the follow-up examination. Standardized testing should be used, and the exact criteria for concluding that a particular subject has normal mental development should be carefully delineated. In order to facilitate comparison of findings across studies, arbitrary groupings should be avoided (e.g., combining patients with normal or mild mental retardation into one category), and, instead, clear groupings based on IQ and/or DQ numerics should be provided.

The most basic unanswered question concerning long-term outcome in this disorder is whether or not any of the current therapeutic modalities, medical or surgical, actually have a beneficial effect with respect to mental/neurological development, later occurrence of other seizure types, or mortality. Furthermore, studies need to be performed to determine if surgical removal of abnormal brain tissue results in long-term developmental improvement independent of seizure control. As reviewed above, the currently available information is widely divergent on these issues, and conflicting reports can not be resolved due to major differences in experimental design and criteria used for assessing outcome. Ethical issues have precluded long-term placebo-controlled studies in this disorder, and there have been no long-term, prospective, studies comparing the relative effectiveness of the major therapeutic approaches. As a result, at the present time it is not possible to separate the possible effects of therapy from the natural course of this disorder.

Appendix 1-A

Percentage of cryptogenic patients in study populations with more than 25 subjects (Data displayed in Chapter 9, Fig 9.1)

	Year	% cryptogenic	Study size
Gibbs et al.	1954	55	237
Druckman and Chao	1955	36	73
Baird and Borofsky	1957	29*	51
Bower	1961	58	33
Harris	1964	17	75
Snyder	1967	63	48
Chevrie and Aicardi	1971	51	78
Fois et al.	1973	45	31
Jeavons et al.	1973	43	150
Gibbs and Gibbs	1976	47	466
Ohtahara et al.	1976	28	94
Seki et al.	1976	44	25
Chevrie and Aicardi	1977	36	230
Chevrie and Aicardi	1978	41	165
Kurokawa et al.	1980	38	757
Curatolo et al.	1981	29	80
Matsumoto et al.	1981a,c	9	200
Riikonen	1982	14	214
Anandam	1983	52	50
Bellman	1983	66	269
Lombroso	1983	42	286
Cavazzuti et al.	1984	39	183
Fois et al.	1984	32	191
Siemes et al.	1984	20	50
Hughes and Long	1986	31	480
Favata et al.	1987	14	58
Rating et al.	1987	15	46
Glaze et al.	1988	13	64
Ito et al.	1990	7	29

Feng et al.	1991	26	105
Prats et al.	1991	31	42
Guzzetta et al.	1993	19	31
Koo et al.	1993	30	57
Ohtahara et al.	1993	10	180
Czochanska et al.	1994	13	91
Schlumberger and Dulac	1994	35	94
Wang et al.	1994	13	30
Haga et al.	1995b	17	42
Chugani and Conti	1996	4	140
Heiskala et al.	1996	20	30
Holden et al.	1997	39	28
Kramer et al.	1997a	10	67
Lortie et al.	1997	58	67
Aydinli et al.	1998	3	143
Chakova et al.	1998	10	42
Kalra and Passi	1998	14	29
Takuma	1998	21	28
Trasmonte and Barron	1998	25	28
Battaglia et al.	1999	27	59
Iinuma	1999	33	43
Koo	1999	24	25
Rantala and Putkonen	1999	20	37
Antoniuk et al.	2000	17	70
Fejerman et al.	2000	29	116
Ohtsuka et al.	2000	12	216
Chiemchanya et al.	2001	39	25
Hwang	2001	38	358
Ito et al.	2001	13	117
Kalra et al.	2001	37	52
Koul et al.	2001	23	44
Liou et al.	2001	16	25
Matsuo et al.	2001a	17	47
Vanhatolo and Riikonen	2001	14	43
Young	2001	23	35
Ito et al.	2002	20	98

* Several cases attributed to vaccination and classified as symptomatic have been included here in the cryptogenic category.

Appendix 1-B

References providing etiological information for Chapter 9

1 Acharya et al., 1997
2 Aicardi, 1986
3 Aicardi et al., 1969
4 Airaksinen, 1974
5 Akiyama et al., 2001
6 Akiyama et al., 1991
7 Aktan et al., 1997
8 Alvarez et al., 1987
9 Amor et al., 2000
10 Anandam, 1983
11 Arai et al., 1997
12 Asanuma et al., 1995
13 Aso et al., 1997
14 Aydinli et al., 1998
15 Badalian et al., 1995
16 Baird and Borofsky, 1957
17 Bakker et al., 1996
18 Bauer and Elger, 1994
19 Baxter, 1999
20 Bellman, 1983
21 Berg, et al., 1999
22 Bignami et al., 1966
23 Billard et al., 1994
24 Bingham et al., 1996
25 Bird, 1987
26 Boor et al., 1992
27 Bouguerra and Bousnuna, 1990
28 Bouhanick et al., 2002
29 Bower and Jeavons, 1959
30 Bower, 1969
31 Bower, 1961
32 Branch and Dyken, 1979
33 Bruyere et al., 1999
34 Buchino et al., 1996
35 Bugiani et al., 1975
36 Cabrera et al., 1998
37 Calderon Gonzalez et al., 1994
38 Canafoglia et al., 2001
39 Cao et al., 1977
40 Caraballo et al., 1998
41 Carmona and Pascual-Castroviejo, 1983
42 Castro-Gago et al., 1993
43 Chakova et al., 1998
44 Chakova, 1996
45 Chao et al., 1957
46 Charlton and Mellinger, 1970
47 Chevrie and Aicardi, 1977
48 Chugani and Conti, 1996
49 Chugani, 1995
50 Ciardo et al., 2001
51 Claes et al., 1997
52 Clancy et al., 1985
53 Coleman, 1971
54 Constantinou et al., 1989

55 Cortez et al., 1997
56 Coulter, 1986
57 Cowan and Hudson, 1991
58 Crichton, 1968
59 Crino et al., 2002
60 Cruz-Velarde et al., 1999
61 Curatolo, 1994
62 Curatolo et al., 1981
63 Curatolo et al., 2001
64 Curatolo et al., 1980
65 Curatolo et al., 1983
66 Cusmai et al., 1993
67 Cusmai, 1994
68 Dalla Bernardina and Dulac, 1994
69 Dalla Bernardina et al., 1979
70 Debard et al., 1979
71 de Grignon and Yunta, 1978
72 de Jong et al., 1976
73 della Rovere et al., 1964
74 Denes et al., 1970
75 Dennis and Bower, 1972
76 Dieker et al., 1969
77 Dolman et al., 1981
78 Druckman and Chao, 1955
79 Duffner and Cohen, 1975
80 Dulac, 1994
81 Dulac and Plouin, 1994
82 Dulac et al., 1993b
83 du Plessis et al., 1994
84 Escofet et al., 1995
85 Fan et al., 1994
86 Feinberg and Leahy, 1977
87 Feingold and Dulac, 1994
88 Feldman and Schwartz, 1968
89 Feng and Liu, 1987
90 Feng et al., 1991
90b Ferraz et al., 1986
91 Fleiszer et al., 1977
92 Fluge, 1975
93 Fois et al., 1994
94 Fois et al., 1973
95 Frochtengarten and Scarante, 1973
96 Frontera Izquierdo et al., 1981
97 Fujikawa et al., 2001
98 Fujimoto et al., 1995
99 Fukuyama and Tsuchiya, 1979
100 Gabriel, 1980
101 Galicchio et al., 1999
102 Falero Gallego et al., 2000
103 Ganesan and Kirkham, 1996
104 Ganji et al., 1987
105 Garaizar et al., 1998
106 Garcia et al., 1978
107 Garcia de Alba et al., 1989
108 Garg and Kleiman, 1994
109 Gedik et al., 1993
110 Gibbs et al., 1954
112 Gold and Freeman, 1965
112b Goldberg-Stern et al., 2001
113 Golden, 1990
114 Grass and Vantman, 1980
115 Gropman et al., 1997
116 Grossi-Bianchi and Pistone, 1968
117 Gudino et al., 2002
118 Guerrini and Carrozzo, 2001
119 Hadjipanayis et al., 1997
120 Haga et al., 1995b
121 Hagberg, 1984
122 Haglund et al., 1981
123 Hakamada et al., 1979
124 Haltia and Somer, 1993
125 Hamano et al., 1989
126 Hamano et al, 1999
127 Hamano et al., 1991
128 Harada et al., 1996
129 Harden et al., 1991
130 Harper, 1967
131 Harris et al., 1981
132 Hattori et al., 1985
133 Hattori et al., 2000
134 Hausler et al., 2001
135 Heilstedt et al., 2001
136 Herbst and Cohen, 1971
137 Hiraiwa, 1993
138 Hoag et al., 1997
139 Hoefer et al., 1963

140 Hollody and Kollar, 1997
141 Honda et al., 1998
142 Hosoya et al., 1999
143 Howitz and Platz, 1978
144 Howitz, 1980
145 Hoyt, 1979
146 Hrachovy et al., 1988a
147 Hrachovy et al., 1987
148 Hrachovy and Frost, 1989a
149 Hughes and Long, 1986
150 Hunt and Dennis, 1987
151 Hunt, 1983
152 Husain, 2000
152b Huson et al., 1988
153 Hwang, 2001
154 Hwang et al., 1996
155 Incorpora et al., 1999
156 Itokazu et al., 1992
157 Jacobi and Neirich, 1992
158 Jarvela et al., 1993
159 Jellinger, 1970
160 Jellinger, 1987
161 Joh et al., 1991
162 Kalayci et al., 1994
163 Kalmanchey and Halasz, 1990
164 Kalra and Passi, 1998
165 Kamoshita et al., 1970
166 Kanazawa et al., 1991
167 Kao et al., 1991
168 Kasai et al., 1995
169 Katano et al., 1994
170 Kellaway, 1959
171 Kellaway et al., 1983
172 Knott et al., 1987
173 Kobayashi et al., 1994
174 Kobayashi, et al., 2001
175 Koide and Shime, 1993
176 Konishi et al., 1979
177 Koo et al., 1993
178 Koo, 1999
179 Korf et al., 1993
180 Koskiniemi et al., 1989
181 Koul et al., 2001
182 Kramer et al., 1997a
183 Kubo et al., 1999
184 Kuriyama et al., 1988
185 Kurokawa et al., 1980
186 Kurokawa et al., 1976
187 Kurokawa et al., 1981
188 Kuwahara et al., 1996
189 Kuzniecky et al., 1994
190 Kwa et al., 1995
191 Lahat et al., 1992
192 Langlais et al., 1991
193 Larregue et al., 1977
194 Leonard et al., 1981
195 Liou et al., 2001
196 Livingston et al., 1958
197 Lombroso, 1983
198 Lopez et al., 1991b
198b Lortie et al., 2002
199 Lutschg et al., 1983
200 Maekawa et al., 1979
201 Mahdi et al., 1990
202 Makela-Bengs et al., 1995
203 Maki et al., 1979
204 Malone et al., 1975
205 Mariani et al., 1984
206 Markand et al., 1982
207 Martin Blazquez et al., 1988
208 Mateos Gonzalez et al., 2000
209 Matsui et al., 1992
210 Matsumoto et al., 1981a
211 Matsumoto et al., 1992
212 Matsumoto et al., 1981b
213 Matsuo et al., 2001a,b
214 Mattyus et al., 1977
215 McShane et al., 1990
216 Meencke, 1985
217 Menezes et al., 1994
218 Mikaeloff et al., 2000
219 Millichap, 1987
220 Millichap et al., 1962
221 Minn et al., 2002
222 Mitsudome et al., 1997
223 Miura et al., 1998

224 Miyazaki et al., 1998
225 Miyazaki et al., 1992
226 Miyazaki et al., 1994b
227 Mizuguchi et al., 2001
228 Mizugishi et al., 1998
229 Mizuguchi and Takashima, 2001
230 Mizukawa et al., 1992
231 Montelli et al., 1981
232 Montelli et al., 1984
233 Mori et al., 1993
234 Mori et al., 1994
235 Mota et al., 1984
236 Motte et al., 1993
237 Muroi et al., 1996
238 Nagamitsu, 1993
239 Nagamitsu et al., 2001
240 Naito et al., 2001
241 Naito et al., 1999
242 Neville, 1972
243 Nevin and Pearce, 1968
244 Nieto et al., 1996
245 Nieto-Barrera et al., 1977
246 Nieto-Barrera et al., 1999
247 Nolte et al., 1988
248 Numabe et al., 2001
249 Oates and Stapleton, 1971
250 Oates and Harvey, 1976
251 Ohtahara et al., 1993
252 Ohtaki et al., 1987
253 Ohtani et al., 1994
254 Ohtsuka et al., 1993
254b Ohtsuka et al, 1998
255 Ohtsuka et al., 1982
256 Ohtsuka et al., 2000
256b Ohtsuka et al., 2002
257 Okumura et al., 1996
258 Okumura and Watanabe, 2001
259 Okumura et al., 2001
260 Otani et al., 1990
261 Otero et al., 1995
262 Ou et al., 1995
263 Ozawa et al., 1998
264 Ozek et al., 1995
265 Paladin et al., 1989
266 Palm et al., 1986
267 Palmini et al., 1991
268 Pampiglione and Moynahan, 1976
269 Parmeggiani et al., 1990
270 Pascual-Castroviejo et al., 2001
271 Pascual-Castroviejo et al., 1998
272 Paterson, 1998
273 Pavone et al., 1991
274 Pavone et al., 1985
275 Pavone et al., 1980
276 Pavone et al., 1993
277 Pietz et al., 1993
278 Pineda et al., 2000
279 Plomp et al., 2000
280 Pollack et al., 1978
281 Pueschel et al., 1991
282 Raas-Rothschild et al., 2002
283 Rail, 1963
284 Rajab et al., 2000
285 Ramenghi et al., 1996
286 Rantala et al., 1996
287 Rantala et al., 2000
288 Rating et al., 1987
288b Reiter et al., 2000
289 Remes et al., 1992
290 Riikonen et al., 1997
291 Riikonen, 1978
292 Riikonen and Simell, 1990
293 Riikonen, 1982
294 Riikonen, 1993
295 Riikonen and Donner, 1979
296 Riikonen, 1995
297 Riikonen, 1994
298 Riikonen, 2001b
299 Riikonen et al., 1999
300 Rizzuto and Ferrari, 1968
301 Roccella and Parisi, 1999
302 Romano et al., 1990
303 Roos et al., 1987
304 Ross, 2002
305 Roth and Epstein, 1971
306 Rufo et al., 1997

307 Ruggieri et al., 1989
308 Rugtveit, 1986
309 Sakuta et al., 1989
310 Salonen et al., 1991
311 Salonga et al., 2001
312 Sankar et al., 1995
313 Sasaki et al., 1999
314 Sasaki et al., 1991
315 Schiffmann et al., 1993
316 Schimschock et al., 1969
317 Schlumberger and Dulac, 1994
317b Appleton, 1995
317c Scheffer et al., 2002
318 Schropp et al., 1994
319 Sfaello et al., 2000
319b Shah et al., 2002
320 Shepherd et al., 1995
321 Sher and Sheikh, 1993
322 Shevell et al., 1996
323 Shields et al., 1995
324 Siemes et al., 1984
325 Silva et al., 1996
326 Silverstein and Johnston, 1984
327 Simonsson, 1972
328 Singer et al., 1980
329 Smilari et al., 2001
330 Smith et al., 1996
331 Soetomenggolo, 1988
332 Somer, 1993
333 Somer and Sainio, 1993
334 Somer et al., 1993
335 Sorel, 1985
336 Sotero de Menezes and Rho, 2002
337 Stafstrom and Konkol, 1994
338 Stafstrom et al., 1991
339 Stamps et al., 1959
340 Stanescu-Segall and Stanescu, 1997
341 Staudt et al., 1994
342 Steinlin et al., 1998
343 Stern et al., 1968
344 Stibler et al., 1999
345 Stromme et al., 1999
346 Suastegui et al., 2001
347 Sugai et al., 2001
348 Sugie et al., 1989
349 Suzuki et al., 1999b
350 Suzuki et al., 1997
351 Sztriha et al., 1994
352 Tagawa et al., 1989
353 Tagawa et al., 1994a
354 Tagawa et al., 1994b
355 Taggard and Menezes, 2000
356 Takuma, 1998
357 Tatsuno et al., 1984
358 Tatzer, 1987
359 Tay et al., 2001
360 Tekgul and Tutuncuoglu, 2000
361 Tjiam et al., 1978
362 Toga and Gambarelli, 1982
363 Topcu et al., 2002
364 Toribe et al., 2001
365 Trasmonte and Barron, 1998
366 Trinka et al., 2001
367 Troy, 1969
368 Tsao and Ellingston, 1990
369 Tsao et al., 1997
370 Tsao and Westman, 1997
370b Turner et al., 2002
371 Ushijima et al., 1986
372 Vanhatalo and Riikonen, 2000
373 Vanhatalo and Riikonen, 2001
374 Vanhatalo et al., 2002b
375 Vaquerizo et al., 1995
376 Velez et al., 1990
377 Viani et al., 1994a
378 Vigevano et al., 1994
379 Vinters et al., 1992
380 Vinters, 2002
381 Vinters et al., 1999
382 Walther et al., 1987
383 Wang et al., 1998
384 Watanabe et al., 1994
385 Watanabe et al., 1973
386 Watanabe et al., 1982
387 Watanabe et al., 1976
388 Watanabe et al., 1987

389 Watanabe et al., 1999
390 Watanabe, 1998
391 Webb et al., 1996
392 Wieczorek et al., 1996
393 Willis and Rosman, 1980
394 Wong, 2001
395 Wyllie et al., 1996b
396 Yamagata et al., 1990
397 Yamamoto et al., 1985
398 Yamamoto et al., 1987
399 Yamamoto et al., 1998
399b Yasuhara et al., 1998
400 Yokoyama, 2001
401 Yukizane et al., 1990
402 Zafeiriou et al., 2001
403 Zammarchi et al., 1994
404 Zappella, 1967
405 Zhongshu et al., 2001

Appendix 2

Therapeutic trials included in Table 11.1

ACTH

Antoniuk et al. 2000
Bower and Jeavons 1961
Chieffi and Fois 1965
Dobbs and Baird 1960
Dreifuss et al. 1986
Feng et al. 1991
Fois et al 1987
Fukazawa 1972
Haga et al. 1992
Harris 1964
Hashimoto et al. 1981
Heiskala et al. 1996
Holden et al. 1997
Hrachovy et al. 1980,1983
Hrachovy et al. 1994b
Ito et al. 1990, 2002
Jeavons and Bower 1964
Kimura et al. 1999
Kvorning and Knudsen 1996
Kohyama et al. 2000
Koide and Shime 1993
Konishi et al. 1992, 1995
Kuriyama et al. 1992
Kusse et al. 1993
Kuwahara et al. 1996
Langlais 1991
Lombroso 1983
Lopez et al. 1991a
Maeda et al. 1997
Maekawa et al. 1979, 1980
Mahdi et al 1990
Millichap et al. 1962
Miyazaki et al. 1992, 1998
Ohtsuka et al. 1983
Pache and Troger 1967
Pauli et al. 1960
Pavone et al. 1985
Rail 1963
Riikonen 1982
Riikonen et al. 1997
Riikonen and Simell 1990
Ross 1986
Ruggieri et al. 1989
Sakuma et al 1980
Satoh et al. 1982
Sher and Sheikh 1993
Shimizu et al. 1990
Sorel 1959
Sorel and Dusaucy-Bauloye 1958
Stamps et al 1959
Sugai et al. 2001
Takahashi et al. 1990
Tekgul et al 1999
Trojaberg and Plum 1960
Vigevano and Cilio 1997
Waltregney 1972
Willoughby et al 1966
Yamamoto et al. 1998
Yanagaki et al. 1999
Yoshioka et al. 1994
Young 2001
Zeharia et al. 1987

ACTH (high dose)

Baram et al. 1996
Chevrie and Aicardi 1971
Cossette et al. 1999
Hrachovy et al. 1994b
Koo et al. 1993
Liebling et al. 1993
Nolte et al. 1988
Riikonen 1982
Riikonen et al. 1989
Riikonen and Perheentupa 1986
Rutledge et al. 1989
Snead et al. 1983,1989

Corticosteroid

Allen 1961
Antoniuk et al. 2000
Baram et al. 1996
Bower and Jeavons 1961
Chiron et al. 1997
Crowther 1964
Danielsen 1965
Farwell et al. 1984
Fukazawa 1972
Hancock and Osborne 1998
Hrachovy et al. 1979, 1983
Jeavons and Bower 1964
Klein 1970
Lombroso 1983
Low 1958
Mikaeloft et al. 2000
Millichap et al. 1962
Nolte et al. 1988
Palmini et al. 1991
Pauli et al. 1960
Snead et al. 1983
Yamamoto et al. 1998
Yoshioka et al. 1994

Vigabatrin

Aicardi et al. 1996
Antoniuk et al. 2000
Appleton et al. 1999
Chiron et al. 1991, 1997
Coppola 1997
Cossette et al. 1999
Elterman et al. 2001
Fejerman et al. 2000
Gaily et al. 2001
Granstrom 1999
Jambaque et al. 2000
Kankirawatana et al. 2002
Koo 1999
Kwong 1997
Lopez-Valdes et al. 1996
Mitchell and Shaw, 2002
Nabbout et al., 2001
Pineda et al. 2000
Prasad et al. 2001
Rufo et al. 1997
Sfaello et al. 2000
Siemes et al. 1998
Tay et al. 2001
Vigevano and Cilio 1997
Villeneuve et al. 1998
Visuditbhan et al. 1999
Vles et al. 1993
Wohlrab et al. 1998
Zubcevic et al. 1999

Nitrazepam

Antoniuk et al 2000
Chamberlain 1996
Dreifuss et al. 1986
Fukushima et al. 1968
Gibbs and Anderson, 1965
Hagberg 1968
Jan et al. 1971
Sfaello et al. 2000
Volzke et al. 1967
Weinmann 1967a,b

Valproate

Amano et al. 1990
Antoniuk et al. 2000
Bachman 1982
Barnes and Bower 1975
Dulac et al. 1986a
Dyken et al. 1985
Holden et al. 1997
Nolte et al. 1988
Ohtsuka et al. 1992
Pavone et al. 1981
Pavone and Incorpora 1985
Siemes et al. 1988

Pyridoxine (Vitamin B_6)

Blennow and Starck 1986
Fois et al. 1987
Heiskala et al. 1996
Hirai et al. 1998
Izuora and Iloeje 1989
Jeavons and Bower 1964
Koide and Shime 1993
Kurlemann et al. 1997
Ohtsuka et al. 2000
Pietz et al. 1993
Takuma 1998
Toribe 2001

Surgery

Adelson et al. 1992
Branch and Dyken 1979
Chugani et al. 1990, 1993
Dolman et al 1981
Hoffman, 2001
Kramer et al. 1997a
Mimaki et al. 1983
Ozkara et al. 2000
Palm et al. 1988
Pinard et al 1993
Ruggieri et al. 1989
Shields et al., 1990
Spiegel et al., 1958
Uthman et al. 1991
Wyllie et al. 1996a,b

Clonazepam

Carson and Gilden 1975
Dummermuth and Kovacs 1973
Hanson and Menkes 1972
Martin and Hirt 1973

Nogen 1978
Nolte et al. 1988
Pavone et al. 1985
Sakuma et al 1980
Vasella et al. 1973

Immunoglobulin

Ariizumi et al. 1983, 1987
Echenne et al. 1991
Espinosa-Zacarias et al., 2002
Shiihara et al. 1984
van Engelen et al. 1994

TRH (thyrotropin-releasing hormone)

Matsumoto et al. 1987, 1989
Takeuchi et al. 1999, 2001

Zonisamide

Hikima et al. 1993
Kawawaki et al. 1999
Kishi et al. 2000
Suzuki et al. 1997
Suzuki 2001
Yanagihara et al. 1995
Yanai et al. 1999

Topiramate

Glauser et al. 1998, 2000
Herranz 2000
Hwang (in Glauser et al. 2000)
Philipi et al., 2002
Thijs et al., 2000

Lamotrigine

Cianchetti et al., 2002
Franz et al. 2001
Mikati et al., 2002
Schlumberger et al. 1994
Veggiotti et al. 1994

Felbamate

Cilio et al. 2001
Hosain et al. 1997
Hurst and Rolan 1995

Appendix 3

Selected studies providing long-term outcome data

(>24 patients/study; both cryptogenic and symptomatic cases; population not selected by etiological or diagnostic factors; duplicate or overlapping series included only once)

Part 1

(Study size, diagnostic status, mortality and development)

Study	# subjects	% crypto.	% deaths	% dev. normal
Antoniuk et al. 2000	70	17		
Battaglia et al. 1999	59	27	7	22
Caplan et al. 1999	29			
Cavazzuti et al. 1984	183	39	8	17
Cebrero Garcia et al. 1990	31			30
Chadwick et al. 2001	25		20	15
Chakova et al. 1998	42	10	7	10
Chevrie and Aicardi 1971	78	51		14
Chevrie and Aicardi 1978	165	41	8	20
Chiemchanya et al 2001	25	39		20
Curatolo et al. 1986	101		5	3
Czochanska et al. 1994	91	13	10	23
Favata et al. 1987	58	14	5	
Fejerman et al. 2000	116	29		
Ferraz et al. 1986	66			15
Fois et al. 1984	191	32	5	19
Tsuchiya and Fukuyama 1978	81		7	16
Gibbs and Gibbs 1976	466	47		15
Glaze et al. 1988	64	13	5	5
Guzzetta et al. 1993	31	19	6	29
Haga et al. 1995a	42	17		
Haginoya et al. 2000	26			35

Study	# subjects	% crypto.	% deaths	% dev. normal
Harris 1964	75	17		8
Heiskala et al. 1996	30	20		20
Holden et al. 1997	28	39	29	8
Hwang 2001	358	38		25
Iinuma 1999	43	33		23
Ito et al. 2001	117	13	2	
Ito et al. 1990	29	7		7
Ito et al. 2002	98	20		6
Jeavons et al. 1973	150	43	22	
Kalra et al. 2001	52	37		17
Koo et al. 1993	57	30	2	
Koul et al. 2001	44	23	2	14
Kramer et al. 1997b	49			6
Kramer et al. 1997a	63		11	7
Kumagai et al. 2001	120			
Kurokawa et al. 1982	27		41	
Lombroso 1983	286	42	11	11
Lortie et al. 1997	67	58		
Madge et al. 1993	206		12	12
Matsumoto et al. 1981b	200	9	19	12
Matsuo et al. 2001a	47	17		11
Mizutani 1969	195		14	17
Ohtahara 1984	25		19	
Ohtahara et al. 1976	94	28		18
Okumura et al. 1998	77			
Pache and Troger 1967	75		20	9
Prats et al. 1991	42	31		28
Rantala and Putkonen 1999	37	20	5	16
Riikonen 2001a	214	15	31	17
Sakuma et al. 1980	46		13	22
Seki et al. 1976	25	44	0	20
Singer et al. 1982	71			11
Singer et al. 1980	55		2	

Study	# subjects	% crypto.	% deaths	% dev. normal
Snyder 1967	48	63		21
Suzuki et al. 1986	38			
Takahashi et al. 1990	33		6	24
Tatzer et al. 1981	35			
Thornton and Pampiglione 1979	100		24	11
Trojaborg and Plum 1960	30		23	0
Wang et al. 1994	30	13		27
Wasser et al. 1983	50			16
Wohlrab et al. 1998	28			25
Wong 2001	105		9	10
Young 2001	35	23		14

Part 2

(Seizures, EEG abnormalities, Lennox-Gastaut syndrome, and neurological deficits)

Study	% with seizures	EEG abnor.	L-G synd.	Neuro. deficit
Antoniuk et al. 2000	26			
Battaglia et al. 1999	40			
Caplan et al. 1999	55			
Cavazzuti et al. 1984	27		14	33
Cebrero Garcia et al. 1990		68	16	
Chadwick et al. 2001	40	55		
Chakova et al. 1998	31		17	
Chevrie and Aicardi 1971				
Chevrie and Aicardi 1978				27
Chiemchanya et al 2001	56			
Curatolo et al. 1986	74			
Czochanska et al. 1994	46		6	41

Study	% with seizures	EEG abnor.	L-G synd.	Neuro. deficit
Favata et al. 1987				
Fejerman et al. 2000	61			
Ferraz et al. 1986				
Fois et al. 1984	40			
Tsuchiya and Fukuyama 1978				
Gibbs and Gibbs 1976		84		
Glaze et al. 1988	53			
Guzzetta et al. 1993	52			
Haga et al. 1995a	67			
Haginoya et al. 2000	30			
Harris 1964				
Heiskala et al. 1996	57			
Holden et al. 1997	84			
Hwang 2001	36			
Iinuma 1999	51		0	
Ito et al. 2001	74		33	
Ito et al. 1990	52			
Ito et al. 2002	48			
Jeavons et al. 1973	55	45		
Kalra et al. 2001				
Koo et al. 1993	51			60
Koul et al. 2001	76			
Kramer et al. 1997b				
Kramer et al. 1997a	63			
Kumagai et al. 2001	40			
Kurokawa et al. 1982				
Lombroso 1983		61	23	
Lortie et al. 1997	9			
Madge et al. 1993	57			60
Matsumoto et al. 1981b				
Matsuo et al. 2001a	55			
Mizutani 1969				
Ohtahara 1984	56			
Ohtahara et al. 1976	47		54	
Okumura et al. 1998	45		3	

Study	% with seizures	EEG abnor.	L-G synd.	Neuro. deficit
Pache and Troger 1967				
Prats et al. 1991	51		21	
Rantala and Putkonen 1999			27	
Riikonen 2001a	67	23	18	
Sakuma et al. 1980	37		4	
Seki et al. 1976	44	92	8	
Singer et al. 1982				
Singer et al. 1980				
Snyder 1967	56			
Suzuki et al. 1986	29			
Takahashi et al. 1990				
Tatzer et al. 1981	57			
Thornton and Pampiglione 1979				
Trojaborg and Plum 1960				
Wang et al. 1994	53			
Wasser et al. 1983				
Wohlrab et al. 1998	36			
Wong 2001	86		12	
Young 2001	63			

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